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Public health burden of diabetes in Ireland: time trends, determinants of complications and the implementation of a public health intervention to improve health outcomes for people with diabetes

A thesis submitted to the National University of Ireland, Cork
for the degree of Doctor of Philosophy in the Department of
Epidemiology and Public Health, School of Medicine.



July 2017

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LIST OF ABBREVIATIONS

ABBREVIATION	TERM
ADA	American Diabetes Association
AR	Attributable risk
ATC	Anatomic Therapeutic Classification codes
BMI	Body Mass Index
C	Context
CAPi	Computer Assisted Personal Interview
CI	Confidence Interval
CMOC	Context-Mechanism-Outcome Configuration
CODEIRE	Cost of Diabetes in Ireland Study
CSO	Central Statistics Office
CVD	Cardiovascular disease
DALY	Disability Adjusted Life Year
DR	Diabetic retinopathy
EAG	Expert Advisory Group for Diabetes
FPG	Fasting Plasma Glucose
HbA1c	Haemoglobin A1c
IDF	International Diabetes Federation
IPAC	International Physical Activity Questionnaire
IQR	Inter quartile range
IRR	Incident rate ratio
M	Mechanism
NCBI	National Council for the Blind of Ireland
NCD	Non-communicable disease
NCPD	National Clinical Programme in diabetes
NHANES	National Health and Nutrition Examination Survey
O	Outcome
OAR	Ophthalmic assessment report
OHA	Oral hypoglycaemic agent
PAR	Population attributable risk
PRISMA	Preferred Reporting Items for Systematic Reviews
QNHS	Quarterly National Household Survey
RR	Relative risk
SD	Standard deviation
SES	Socio-economic status
SLÁN	Survey on Lifestyle and Attitudes to Nutrition in Ireland
SR	Self-report
TIA	Transient Ischemic Attack
TILDA	The Irish Longitudinal Study of Ageing
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
USA	United States of America
WC	Waist circumference
WHO	World Health Organisation

DECLARATION

I declare that this thesis has not been submitted as an exercise for a degree at this or any other University. The work, upon which this thesis is based, was carried out in collaboration with a team of researchers and supervisors who are duly acknowledged in the text of the thesis. The Library may lend or copy this thesis upon request.

Signed:

Date:

DEDICATION

For Lucy,

You are my sunshine.

ACKNOWLEDGEMENTS

I finally made it!! It has been a long road, my journey in education began 13 years ago on a FETAC level 3 course, and I had no idea that it would lead me to where I am today. My teachers often wrote on my report card '*Marsha would do very well if she would only apply herself*', it took a while but I believe they were right!

First, I would like to express my sincere thanks to my supervisory team. Over the past few years you have all contributed to getting my PhD over the line; it is difficult to express my gratitude in words. To Professor Patricia Kearney, thank you for giving me the opportunity to undertake the PhD. Your ongoing support and guidance have been invaluable, you truly are an inspiration. It has been a pleasure, and a privilege, working with you on the Leader Award. The knowledge and experience which I have gained throughout my time on the project will prove to be an invaluable asset. To Dr Sheena McHugh, thank you for your expertise, motivation and your endless patience. I really appreciate the guidance you have given me over the course of the PhD. To Dr Tony Fitzgerald, thank you for your encouragement and advice from the beginning of the PhD. It was a pleasure working alongside you as a tutor. To Dr Claire Buckley, you were always so positive and enthusiastic about my work, thank you, it provided me with the motivation to keep going. To Dr Ronan Canavan, thank you for sharing your knowledge and expertise, I appreciate you taking the time to point me in the right direction.

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*“If you can find a path with no
obstacles, it probably doesn't lead
anywhere.”*

Frank Clark

THESIS ABSTRACT

Background and Aim

Diabetes is a serious global public health issue. Diabetes-related complications are a significant source of morbidity, premature mortality and a major contributor to health care costs. Understanding the epidemiology of diabetes and related complications is essential to identify public health priorities for planning and tackling the problem. This includes identifying possible contributing factors to prevent and delay the onset of diabetes related complications. Blindness due to diabetic retinopathy is a serious complication of diabetes which is potentially preventable by adequate risk factor control, early detection and timely treatment. In 2013, a national diabetic retinopathy screening programme (Diabetic Retinascreen) was introduced in Ireland. Reliable data are needed to evaluate and assess the implementation of this service and its potential for future impact. The aim of this thesis was to estimate the public health burden of diabetes in Ireland including time trends and determinants of complications and to investigate the implementation of a public health intervention for people with diabetes.

Methods

Data from four nationally representative studies, identified by a systematic review, were used to explore trends in diagnosed diabetes prevalence between 1998 and 2015. Cross-sectional analysis of data from the first wave of The Irish Longitudinal Study on Ageing (TILDA) (2009–2011) was carried out to estimate the prevalence of diagnosed type 2 diabetes and its related complications in adults aged 50 years and over; determinants of macro-and microvascular complications were identified. Trends of visual impairment and blindness due to diabetic retinopathy in adults aged

18–69 years over a decade were described using data from the National Council for the Blind of Ireland, (2004–2013) and changes in rates were explored. The final study, a realist evaluation with an iterative mixed-methods design, was carried out to investigate the implementation and uptake of Diabetic Retinascreen.

Results

In adults aged 18 years and over, the national prevalence of doctor diagnosed diabetes significantly increased from 2.1% in 1998 to 5.2% in 2015. The prevalence of diabetes complications varied depending on study population and methodology used.

In TILDA, diagnosed type 2 diabetes prevalence was 8.4%. Among participants with diagnosed type 2 diabetes, the overall prevalence of macrovascular complications was 15.1% and the overall prevalence of microvascular complications was 26.0%. Older age, being male, a history of smoking, a lower level of physical activity, and a diagnosis of high cholesterol were independent predictors of macrovascular complications. Diabetes diagnosis of 10 or more years, a history of smoking, and a diagnosis of hypertension were associated with an increased risk of microvascular complications. Older age, third-level education, and a high level of physical activity were protective factors.

Over a decade, the incidence of visual impairment due to diabetic retinopathy increased in both the total population and the population with diagnosed diabetes. In contrast, the incidence of blindness due to diabetic retinopathy in the total population did not significantly change during the study period. The annual incidence in the population with diabetes varied between years (31.9 per 100,000 [95% CI 21.6-

45.7] in 2004 to 14.9 per 100,000 [95% CI 8.2-25.1] in 2013) however, there was no evidence of a linear trend.

The evaluation of the initial implementation of the Diabetic Retinascreen programme indicated that over a 14 month period, a total of 63% of people with diabetes attended screening. The refined theory of how the programme worked was that people were more likely to consent when they perceived that the service was a relevant to them and had a relative advantage over existing services. This reaction was triggered in a context where people heard about Diabetic Retinascreen from a trusted and familiar person and were dissatisfied with existing services. Furthermore they perceived their own risk of diabetic retinopathy to be high and understood the purpose of screening. Once consented, people were more likely to attend their screening appointment with Diabetic Retinascreen because personal and service flexibility made access seem easy.

Conclusions: Research in this thesis is an important contribution to our understanding of the public health burden of diabetes in Ireland. In the absence of a national diabetes register, findings provide robust estimates on the trends in the incidence and prevalence of diagnosed diabetes and its complications among adults aged 18 years and over. Findings have provided a key source of information to facilitate diabetes program planning and to inform policy decisions, including resource allocation. In Ireland, the population at risk is increasing each year therefore maximising uptake of diabetic retinopathy screening must be a priority.

1. INTRODUCTION

1.1 Introduction

Diabetes is a serious global public health issue which has been described as the most challenging health problem in the 21st century (1, 2). Cases of diabetes have progressively increased worldwide (3); driven primarily by rising levels of obesity and ageing populations (2, 4). Diabetes places a substantial burden on the individual, society and the economy. Much of this burden is attributable to the macrovascular (myocardial infarction, congestive cardiac failure, cerebrovascular accident, transient ischaemic attack) and microvascular (diabetic retinopathy, diabetic neuropathy and diabetic nephropathy) complications of diabetes (5). As the prevalence of diabetes rises, diabetes related complications represent a growing global public health and health service challenge (6).

In response to these challenges, the National Clinical Programme for Diabetes (NCPD) was established in 2010 to *'ascertain and reduce the prevalence of diabetes in Ireland and to reduce the burden of diabetes on both affected individuals and the State by reducing the morbidity and mortality associated with diabetes'* achieved through the reorganization of existing services and the introduction of new services and supports for people with diabetes (7). Dedicated work streams were established for the implementation of a national diabetic retinopathy screening programme (Diabetic Retinascreen), a national model of care for the screening and treatment of diabetic foot disease, and a national model of integrated care for the management of diabetes across primary, secondary and tertiary care settings.

Good-quality epidemiological data on the incidence and prevalence of diabetes and related complications are important to support the planning and implementation of

public health policies and programmes, and to determine research priorities (8-12). Within-country data are needed to quantify the population at risk and to monitor trends in the health impacts of diabetes. These data are vital for planning health services and for monitoring the effectiveness of interventions aimed to reduce the burden of diabetes over time (8-12).

Ireland does not have a national diabetes register or universal data-capture system to assess trends of diabetes and related complications. The lack of a unique patient health identifier is a unique limitation in Ireland preventing linkage of individual patient data from various healthcare sources. The Euro Diabetes Index (2014) stated that there was a lack of reliable data to monitor diabetes related complications in Ireland (13).

Trends in the incidence of lower-leg amputations in people with diabetes over a five year period were recently reported (14); however, contemporary data on trends of visual impairment due to diabetic retinopathy are lacking. In 2010, the World Health Organisation (WHO) highlighted the importance of within-country data on visual impairment to facilitate global efforts aimed at monitoring and eliminating avoidable blindness (15). The introduction of a national retinopathy screening programme (Diabetic Retinascreen) in 2013 provides an opportunity for the first time to monitor rates of blindness. However, uptake has been highlighted as a concern nationally and internationally. Additionally, the early implementation stage of Diabetic Retinascreen highlighted programme uptake as a concern. Hence, there is an urgent need to explore this further to provide formative information for the future roll out of the programme.

1.2 Aim

The overarching aim of this thesis was:

To estimate the public health burden of diabetes in Ireland including time trends and determinants of complications and to evaluate the implementation of a public health intervention to prevent and delay the development of a complication for people with diabetes.

1.3 Objectives

Specifically, the objectives were:

1. To systematically identify and summarise studies describing the prevalence of diabetes and the most common macrovascular and microvascular complications among adults aged 18 years and over in Ireland between 1998 and 2014 and to describe trends in diagnosed diabetes prevalence between 1998 and 2015.
2. To estimate the prevalence of diagnosed type 2 diabetes among adults aged 50 years and over and to determine the prevalence of macrovascular and microvascular and complications in those with diagnosed type 2 diabetes.
3. To identify the determinants of macrovascular and microvascular complications among adults aged 50 years and over with diagnosed type 2 diabetes.

4. To describe trends in the incidence of visual impairment and blindness due to diabetic retinopathy over a ten-year period (2004–2013) and to explore whether these rates changed over time.
5. To carry out a theory-driven evaluation of the initial uptake of Diabetic Retinascreen to understand how the programme was working, for whom and in what circumstances.

1.4 Research setting

1.4.1 Describing the public health burden of diabetes and related complications among adults age 18 years and over in Ireland

The following existing national datasets were obtained for secondary analysis in this research (Chapters 3-6): the National Survey of Health and Lifestyles in Ireland (SLÁN) (16-18), The Irish Longitudinal Study on Ageing (TILDA) (19) and the National Council for the Blind in Ireland (NCBI) (20).

1.4.2 Understanding the uptake of the national retinopathy screening programme: a realist evaluation

This study is original research using primary data collection and analysis. Data were collected as part of a wider on-going evaluation of the NCPD which is adopting a realist approach. The overall evaluation is examining the implementation of three on-going work streams of the NCPD: the national model of foot care for people with diabetes; the national model of integrated care for diabetes and the national diabetic retinopathy screening programme. The study protocol has been published in *Implementation Science* (21) (Appendix 1).

1.5 Thesis outline

This thesis contains eight chapters, five of which are studies addressing the aims and objectives outlined above. Figure 1 illustrates the five studies and the corresponding chapters.

Chapter 2 provides a brief introduction to the extent of the problem of diabetes and related complications. Recommendations to address this problem, including retinopathy screening programmes, are reviewed and factors that determine screening attendance are explored.

A systematic review was undertaken which describes trends in the prevalence of doctor diagnosed diabetes among adults in the Republic of Ireland between 1998 and 2015 (Chapter 3). The rationale for carrying out this systematic review was to highlight current gaps in existing knowledge; findings from this paper informed the research for this thesis. These data had not been systematically collated prior to this thesis being undertaken.

Chapter 4 investigates the prevalence of diagnosed type 2 diabetes and four macrovascular complications (myocardial infarction, congestive cardiac failure, cerebrovascular accident, transient ischaemic attack) and five microvascular complications (leg ulcer, proteinuria, diabetic neuropathy, diabetic retinopathy, diabetic nephropathy) among a nationally representative sample of adults aged 50 years and over in Ireland. Individual level determinants of these complications are explored in Chapter 5. Individual factors assessed are age, gender, educational attainment, smoking, physical activity, and previous diagnosis of hypertension and high cholesterol.

Chapter 6 investigates rates of visual impairment and blindness due to diabetic retinopathy in the total population and the population with diabetes in the Republic of Ireland. Data obtained from the NCBI were used as the numerator and data on the population at risk were based on prevalence figures calculated in Chapter 3.

Uptake of Diabetic Retinascreen is examined in Chapter 7. Factors which influence the decision to participate (or not) in the national diabetic retinopathy screening programme are explored among people with diabetes who were eligible to use this service over a 14-month period.

Chapter 8 provides an overall discussion of the main findings, the strengths and limitations of this thesis and makes suggestions for future research.

This PhD project is presented in the format of a collated thesis, comprised of a series of publications in peer-reviewed academic journals. Chapters 3, 4, 5 and 6 have been published. Chapter 7 is being prepared for publication at the time of printing of the thesis.

Aim: To estimate the public health burden of diabetes in Ireland including time trends and determinants of complications and to evaluate the implementation of a public health intervention to prevent and delay the development of a complication for people with diabetes.

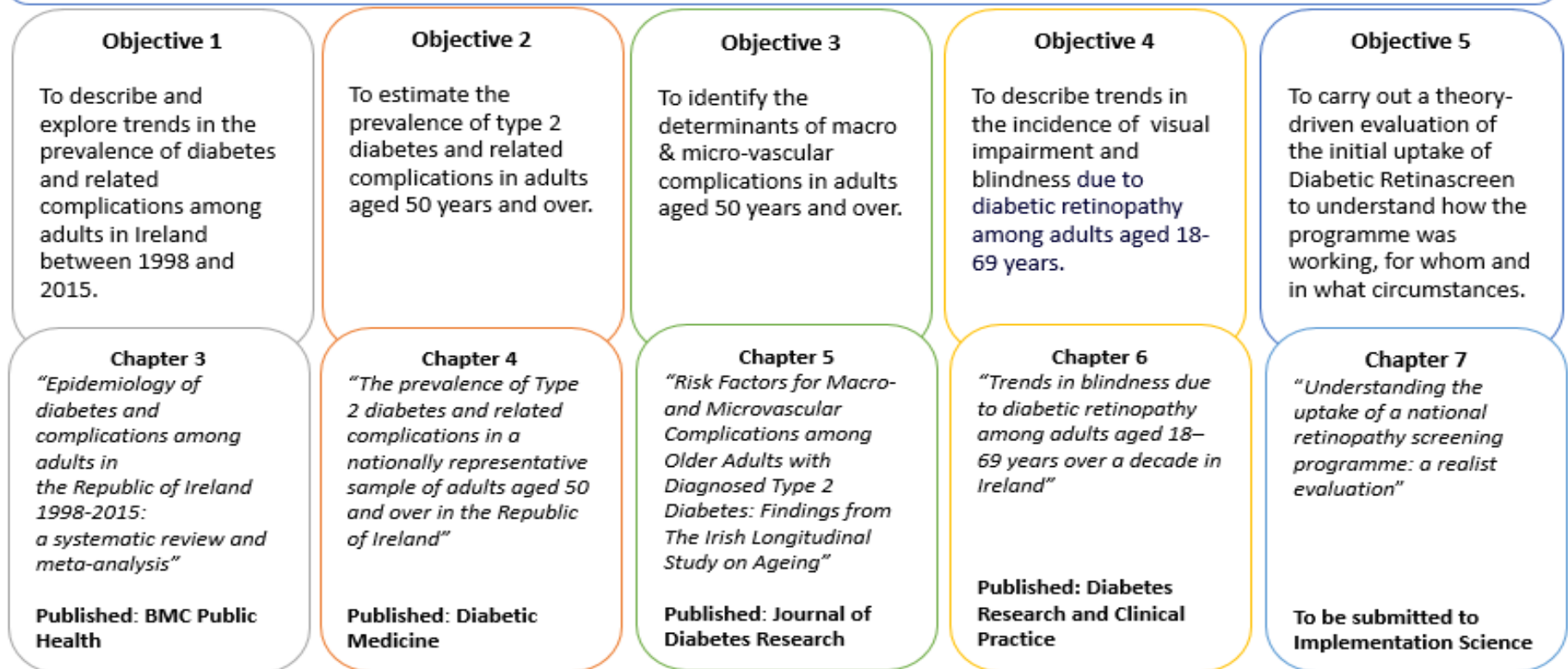


Figure 1. Overview of thesis including aims and objectives

1.6 Conceptual Framework

The conceptual framework for the research in this thesis is based the '*measurement iterative loop*' which was developed by Tugwell et al., 1985 (12) (Figure 2).

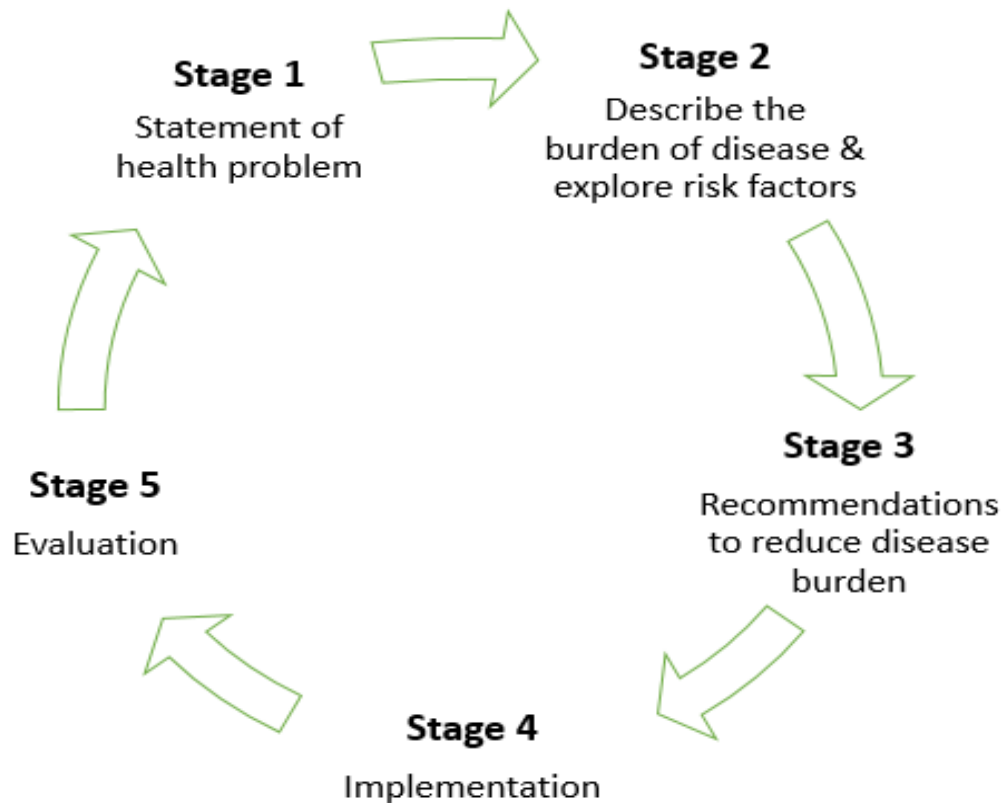


Figure 2. Measurement iterative loop

The framework consists of an iterative cycle of five stages for assembling health information and evaluating public health interventions. Each stage underpins each chapter of this thesis (Table 1) and place the individual studies in context. Using the framework allows for the systematic identification of areas in which further research is needed. The iterative loop or similar approaches have been applied in a variety of areas such as the management of the diabetic foot (22), technology assessment (23), cancer control (24), policy development (25) and paediatric emergency medicine (26).

Table 1. Steps in the measurement iterative loop

Step	Questions	Thesis chapter
1: Statement of the public health issue	<ul style="list-style-type: none"> • What is diabetes? • Why is diabetes a public health issue? 	<ul style="list-style-type: none"> • Chapter 2
2: Describe the public health burden of disease and explore risk factors	<ul style="list-style-type: none"> • What is the public health burden of diabetes and related complications in Ireland? • What are the trends of diabetes and related complications in Ireland? <ul style="list-style-type: none"> - Have these trends changed over time? • What are the risk factors for diabetes complications? 	<ul style="list-style-type: none"> • Chapters 3-6
3: Recommendations to reduce disease burden	<ul style="list-style-type: none"> • What works to reduce the public health burden of visual impairment due to diabetic retinopathy? 	<ul style="list-style-type: none"> • Chapter 2
4: Implementation of recommendation	<ul style="list-style-type: none"> • How was uptake of the national diabetic retinopathy screening programme expected to work? 	<ul style="list-style-type: none"> • Chapter 7
5: Evaluation of public health programme	<ul style="list-style-type: none"> • How is uptake of the national diabetic retinopathy screening programme working in practice? 	<ul style="list-style-type: none"> • Chapter 7

1.7 Author's contribution

I was the lead author of all of the papers contained in this thesis. This involved the formulation of the research question for each chapter, conducting literature searching, data collection, data management, data analysis and drafting of each manuscript. A summary of my role in each Chapter is provided in Appendix 2.

2. BACKGROUND

This chapter provides a brief overview of diabetes and related complications. First, diabetes as an important public health issue is considered. Second, the extent of the problem globally is described. Third, health consequences of diabetes and determinants of complications are outlined. Next, to place Chapters 6 and 7 in context, the focus then moves to one serious microvascular complication, diabetes retinopathy, providing a summary of international rates and considers diabetic retinopathy screening programmes as an effective public health intervention. Finally, factors which determine attendance at such programmes are described.

2.1 What is diabetes?

Diabetes is a group of chronic metabolic conditions, which are associated with hyperglycaemia, either because the pancreas does not produce enough insulin, or because the body cannot effectively use the insulin that is produced, or both (27). In general, the type of diabetes is categorised into four groups:

1. Type 1 diabetes is characterised by a complete lack of insulin production and accounts for 5% to 10% of all cases;
2. Type 2 diabetes is characterized by insulin resistance or relative insulin deficiency. Type 2 diabetes is the most common form and accounts for approximately 90% of all cases;
3. Gestational diabetes is hyperglycaemia that is first recognized during pregnancy;
4. Other types of diabetes such as maturity-onset diabetes of youth or latent autoimmune diabetes in adults are caused by specific genetic conditions or from surgery, medications, infections, pancreatic disease, or other illnesses and accounts for 1% to 5% of all diagnosed cases (27) .

2.2 Diabetes as an important public health issue

Diabetes is a significant cause of premature mortality and morbidity (5). Over the past number of years, the global public health burden of diabetes has continued to rise (5, 28, 29). Type 2 diabetes is the main driver of the epidemic, accounting for approximately 90% of all cases (2). The increasing burden of diabetes is driven primarily by rising levels of obesity and an ageing population (2, 30).

Between 1990 and 2013, mortality rates for diabetes increased by 9.0% (29). Since 1990, disability due to diabetes has also grown substantially, with particularly large increases among people aged 15–49 years (28). The Global Burden of Disease Study reported that diabetes was the ninth leading cause of mortality in 2013 (29) and the 11th largest cause of disability adjusted life years (DALYs) (31) in 2015. The economic cost of diabetes is also high and will continue to rise; approximately 12% of the world's total health expenditure was spent on diabetes in 2010 (32). The rising public health burden of diabetes has increased interest in the economic and societal costs of diabetes. In 2011, it was declared as one of four priority non-communicable diseases targeted by world leaders who recognised that a large proportion of the impact of diabetes can be prevented or reduced through the introduction of evidence-based interventions (33).

2.3 Trends and prevalence of diabetes

2.3.1 Global trends and prevalence of diabetes

A systematic review examining worldwide trends in diabetes prevalence in 107 countries between 1980 and 2008 concluded that diabetes was a rising global hazard, with the number of adults with diabetes having more than doubled over nearly three decades (3).

Findings from a more recent systematic review confirmed that over the past three decades, the global burden of diabetes had risen substantially in countries at all income levels (34). Using data from 146 countries and 751 population-based studies, the NCD Risk Factor Collaboration reported that between 1980 and 2014 there was a four-fold increase in the number of adults aged 18 years and over with diabetes. Over the period of interest, the worldwide prevalence of diabetes almost doubled in males (4.3% in 1980 to 9.0% in 2014) and increased by 60% in females (5.0% in 1980 to 7.9% in 2014). The authors note a shifting from an excess prevalence in women in 1980, to a higher male prevalence in 2014 (34).

The rising prevalence of diabetes has been attributed to obesity, sedentary lifestyles, population growth and ageing population (2, 4).

2.3.2 Trends and prevalence of diabetes in Europe

In Europe, evidence suggests that the prevalence of diabetes is in line with global trends (35-39). A systematic review predicting trends in type 2 diabetes over a five year period (1995 to 2000) for seven European countries reported a slight decrease in diabetes prevalence in Finland; whereas a significant increase in prevalence was reported for Denmark, Spain, the UK, Germany, Italy and France (35).

Estimates from more recent studies have confirmed that diabetes prevalence has continued to rise. Sharma et al., 2016 (36) extracted data from a national primary care medical records database to examine trends in the prevalence of type 2 diabetes in the UK between 2000 and 2013. The study found that the prevalence more than doubled over the study period, from 2.4% in 2000 to 5.3% in 2013. The prevalence in males was approximately 30% higher than in females and estimates increased linearly with age (36).

Recent estimates from the Scottish Diabetes Survey (2014) reported that the prevalence of diabetes increased from 3.2% to 5.1% in Scotland between 2004 and 2013 (37). Read et al. 2016 (37), explored possible factors for this increase by linking data from the Scottish national diabetes register to mortality records. The study reported that the incidence of type 2 diabetes remained relatively stable after 2004 while mortality rates declined. The authors concluded that declining rates of obesity and a decrease in undiagnosed diabetes prevalence (due to earlier detection of diabetes) have caused incident rates to stabilise and suggest that improved survival is the leading contributor to the increasing diabetes prevalence (37).

Elsewhere in Europe, Pereira et al. 2014 (38) pooled data from 18 national surveys to estimate age and gender-specific prevalence of self-reported diabetes over a 22 year period in Portugal. Between 1987 and 2009, diabetes prevalence remained approximately constant among younger adults (mean age of 30 years), while it increased in middle-aged (mean age 50 years) and older adults (mean age of 70 years). Over this period, there was a three-fold increase in prevalence rates among males and a two-fold increase among females. In 2009, the prevalence of self-reported diabetes was 9.4% and 8.6%, among males and females, respectively. An increase in obesity rates were suggested as possible explanations for the rising prevalence in Portugal (38).

In Italy, Monesi et al., 2011 (39), extracted data from an administrative health database to examine temporal trends in diabetes prevalence among adults between 2000 and 2007. Over the study period, the absolute number of individuals with diabetes increased by 47%, while the total population grew by 6.6%. The study found that diabetes prevalence increased on average, by 4.0% per year, from 3.0% in 2000

to 4.2% in 2007, while incidence rates did not change and mortality rates decreased by 3.0% per year. Ageing population, earlier detection of diabetes and improved survival were suggested as possible explanations for the rise in prevalence.

2.3.3 Trends and prevalence of diabetes in USA

Data from the USA suggest that trends in diabetes prevalence are comparable to estimates from Europe. Menke et al., 2015 (40) used data from the National Health and Nutrition Examination Surveys (NHANES) to examine trends in the prevalence of diabetes (diagnosed, undiagnosed and prediabetes) among adults aged 20 years and over between 1988 and 2012. NHANES is an ongoing panel survey which collects data from nationally representative samples of non-institutionalized adults in the USA (41). Diagnosed diabetes was ascertained by self-report of a previous diagnosis by a doctor or other health professional. Over the study period, the prevalence of diagnosed diabetes increased significantly by 52%, from 6% in 1988-1994 to 9.1% in 2011-2012. This increase was observed among the overall population and within each socio-demographic stratum (i.e. age-group, gender, ethnicity, education level, income level). The authors note that rates of diagnosed diabetes began to stabilise between 2007-2008 and 2011-2012. Improved detection of diabetes, an increase in obesity and an ageing population were suggested as possible explanations for the rise in prevalence (40).

2.3.4 Prevalence of diabetes in longitudinal studies of ageing

The world's population is growing older. Changes in the demographic profile of many countries pose a major public health challenge, which include an increase in the number of people with chronic diseases. These changes will inevitably place rising demands on the health-care system. In response to this challenge, a number of large

longitudinal studies of ageing have been developed in various countries around the world. Findings from these studies are used to plan appropriate health, medical, social and economic policies. The prevalence of diabetes from four longitudinal studies of ageing are summarised in Table 2 to place results from the Irish Longitudinal Study on Ageing, TILDA (Chapter 4) in an international context. Each study includes community dwelling adults aged 50 years and over. Diabetes was ascertained by self-report of a previous diagnosis by a doctor or other health professional.

Table 2. Prevalence of self-reported previous doctor diagnosis of diabetes in four longitudinal studies of ageing

	Total n	Response rate (%)	Diabetes type	Prevalence (%)
Survey of Health, Ageing and Retirement in Europe (2004-2005) ¹⁽⁴²⁾	21,910	62	All	10.9
English Longitudinal Study of Ageing (2002-2003)(43)	11,523	70	All	8.1
USA Health and Retirement Study (2004) ⁽⁴²⁾	18,580	86	All	16.4
The WHO Study on Global Ageing and Adult Health (2007-2010) ²⁽⁴⁴⁾	34,129	75	All	7.2

1: Austria, Belgium, Denmark, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, Switzerland

2: China, Ghana, India, Mexico, Russia, South Africa

2.4 Health impacts of diabetes

Much of the public health burden of diabetes can be attributed to complications that are secondary to diabetes (5). Chronic hyperglycaemia affects multiple organ systems in the body which over time, can lead to vascular complications. Generally, complications from diabetes can be classified as macrovascular or microvascular (5).

2.4.1 Macrovascular complications of diabetes

Macrovascular complications, which affect the large vessels of the circulatory system, include myocardial infarction, congestive cardiac failure, cerebrovascular disease and peripheral vascular disease (5).

Macrovascular complications are a major cause of death and disability in people with diabetes, accounting for 44% of fatalities in people with type 1 diabetes and 52% in people with type 2 diabetes (45, 46). After controlling for traditional CVD risk factors, people with diabetes are two to four times more likely to develop macrovascular complications relative to the general population and have a two-fold increased risk of stroke within the first five years of diagnosis compared with the general population (47, 48).

2.4.2 Microvascular complications of diabetes

Microvascular complications involve damage to the small blood vessels which can result in eye damage (diabetic retinopathy), nervous system damage (diabetic neuropathy) and renal system damage (diabetic nephropathy) (5).

2.4.2.1 Diabetic retinopathy

Diabetic retinopathy causes changes in the blood vessels of the retina that can lead to visual impairment and blindness (49). After 20 years of diabetes, nearly all those with type 1 diabetes and more than two-thirds of those with type 2 diabetes will have some degree of diabetic retinopathy (50).

Diabetic retinopathy is the leading cause of vision loss in adults aged 20–74 years (51). From 1990–2010, it was the fifth most common cause of preventable blindness and also the fifth most common cause of moderate to severe visual impairment (52). Genz et al., 2010 (53) found that the risk of blindness in an individual with diabetes was 2.4 times that of an individual without diabetes. Visual impairment due to diabetic retinopathy has a significant impact on patients' quality of life and can compromise their ability to manage their disease, which in turn can contribute to the occurrence of other diabetic complications and overall life expectancy (54).

2.4.2.2 Diabetic neuropathy

Diabetic neuropathy is nerve damage that is due to diabetes. Up to 50% of people with diabetes develop nerve damage leading to foot ulcers and in severe cases, limb amputation (55).

Diabetic neuropathy is a common cause of lower-leg amputations (49). In the USA, 82% of all vascular-related lower extremity amputations are associated with diabetes (56). In Ireland, Buckley et al., 2012 (14) found that, the risk of an individual with diabetes undergoing lower-leg amputation was 22 times that of an individual without diabetes.

2.4.2.3 Diabetic nephropathy

Diabetic nephropathy is a progressive disease that occurs from damage to small blood vessels in the kidneys leading to the kidneys becoming less efficient or to fail altogether (49).

Diabetic nephropathy occurs in approximately 40% of all people with diabetes and it is a leading cause of chronic kidney disease and end-stage renal disease (57). Kidney disease accounts for 21% of deaths in people with type 1 diabetes and 11% of deaths in people with type 2 diabetes (57, 58).

2.5 Prevalence of macrovascular and microvascular complications

Differences in a number of factors can influence the estimated prevalence of diabetes complications including: the method used to detect complications, the age-range of participants, severity and duration of diabetes and the distribution of risk factors.

The Cost of Diabetes in Europe-Type II study pooled data on 7000 people with type 2 diabetes aged 30 years and over using data from different regions in Europe (Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden and the UK) in 1998 (59). The study found that 72% of people had at least one diabetes-related complication. Among those with macrovascular complications, peripheral vascular disease was the most common, with a prevalence of 18%, followed by congestive cardiac failure (12%) and myocardial infarction (9%). Of those with microvascular complications, diabetic neuropathy was the most common, with a prevalence of 28%, followed by diabetic retinopathy (20%) and diabetic nephropathy (20%). Furthermore, 2% of the sample were blind or had lower-leg amputation, and 1 % had end-stage renal failure requiring dialysis. The estimated annual healthcare cost per individual was €2834; 55% of this cost was attributable to hospital admissions (59).

More recently, the Guideline Adherence to Enhance Care (GUIDANCE) study (60) carried out a cross-sectional analysis to determine the prevalence of macro-and microvascular complications among people with type 2 diabetes aged 18 years and over from eight countries in Europe (Belgium, France, Germany, Italy, Ireland, Sweden, the Netherlands, and the UK), between 2009 and 2010. Data were extracted from medical records in primary and secondary care. In total, 7,597 were included in the sample, of these 56% were male with a mean age of 66.5 years (SD 10.8). The study found that the overall prevalence of macrovascular complications was 24%; which ranged from 15% in Belgium to 38% in the UK. The overall prevalence of microvascular complications was 28%; which ranged from 22% in the UK to 37% in Germany. Prevalence figures for individual complications were not reported (60).

Data from NHANES 1999-2004 were used to assess the prevalence of diabetes-related complications among adults with diagnosed type 2 diabetes aged 20 years and over in the USA (61). Complications were ascertained by self-report of a previous diagnosis by a doctor or other health professional. The study found that approximately two-thirds of people with diabetes had a previous diagnosis of at least one macrovascular or microvascular complication. The most common macrovascular complication was myocardial infarction (9.8%), followed by congestive cardiac failure (7.7%) and cerebrovascular disease (6.6%). The most common microvascular complication was chronic kidney disease (28%), followed by diabetic neuropathy (19%) and diabetic retinopathy (19%) (61).

2.5.1 Prevalence of diabetic retinopathy

Worldwide, it has been estimated that approximately 93 million individuals have some level of diabetic retinopathy and approximately one third are cases of vision-threatening diabetic retinopathy (6). An individual participant meta-analysis of 22,896 adults aged 20 to 79 years from 35 population-based studies in the USA, Australia, Europe and Asia (1980 to 2008) estimated that the overall prevalence of any diabetic retinopathy was 34.6% and for vision-threatening diabetic retinopathy was 10.2% in 2010 (62). Prevalence of any diabetic retinopathy and vision-threatening diabetic retinopathy were similar among males and females and were highest in African Americans and lowest in Asians. Prevalence of any diabetic retinopathy was higher in those with type 1 diabetes, compared to those with type 2 diabetes (77.3 vs. 25.2 %)(62).

Ruta et al., 2013 (63), collated evidence on the prevalence of diabetic retinopathy in 13 developing and 20 developed countries between 1985 and 2012. The systematic

review included data from 72 studies and reported an overall median prevalence of 28%. A wide variation in prevalence was observed between countries (63). In Europe, estimates from population-based studies ranged from 10% in Norway to 37.3% in the UK. Estimates from primary care-based studies ranged from 20% in Spain to 50% in Germany. The authors concluded that the review highlighted inconsistencies between study methodologies and demonstrated that there was a lack of reliable population-based data describing the prevalence of diabetic retinopathy (63).

2.6 Trends in blindness due to diabetic retinopathy

Comparing the incidence of blindness due to diabetic retinopathy between countries is also limited due to differences in blindness criteria, differences in numerators (blindness in diabetes vs. blindness attributable to diabetes) and varying methods to estimate the population at risk. Hall et al. (64) used blind registry data to describe trends in the incidence of blindness due to diabetic retinopathy over a ten year period (2000-2009) among adults with diabetes in Fife, Scotland. A decrease in the crude incidence of blindness attributable to diabetes was observed, from 1.43 to 1.10 per 100,000 total population and 59.7 to 23.9 per 100,000 population with diabetes (64).

Elsewhere in the UK, a study from Leeds used data from visual impairment certification to analyse trends in the incidence of blindness secondary to diabetic retinopathy between 2008 and 2010 (65). In this study, the crude incidence of severe visual impairment decreased from 1.2 to 0.6 per 100,000 total population and 33.5 to 16.9 per 100,000 population with diagnosed diabetes. The crude incidence of sight impairment decreased from 89.2 to 63.0 per 100,000 population with diagnosed diabetes (65).

Trends towards a declining incidence have also been observed in other parts of the UK (66) , Germany (53), Sweden (67), Israel (68, 69) and the USA (11). Downward trends have been attributed to a combination of factors, including improvements in disease management, earlier detection and treatment of diabetic retinopathy through the implementation of standardised retinopathy screening programmes and an increase in the number of diabetes cases (70, 71). It has been suggest that while the rates of some diabetes complications have decreased, the absolute number of cases will continue to rise because of the rising prevalence of diabetes (72). Longer duration of diabetes diagnosis is an established risk factor for diabetic retinopathy (73). After 20 years of diabetes, nearly all individuals with type 1 diabetes and more than two-thirds of individuals with type 2 diabetes will develop some degree of retinopathy (50). Therefore it is possible that the full impact of the diabetes epidemic has not yet been realised.

2.7 Determinants of macrovascular and microvascular complications

2.7.1 Diabetes related factors

Hyperglycaemia and longer diabetes duration are the most common risk factors for diabetes complications (74-84). Diabetes duration reflects total glycaemic control and risk factor exposure over time (85).

2.7.2 Cardiovascular risk factors

Established risk factors for CVD such as hypertension, high cholesterol, and smoking further increase the likelihood of developing macro-and microvascular complications (86). The United Kingdom Prospective Diabetes Study (UKPDS) reported that the risk of myocardial infarction and stroke were higher in smokers and those with high cholesterol (87, 88). Prospective studies have also documented hypertension as a risk factor for the development macrovascular complications among individuals with

type 2 diabetes (87-90). Likewise, both smoking and hypertension have been identified as prominent risk factors in the development of neuropathy, nephropathy and retinopathy (77, 79-81, 89, 91).

2.7.3 Socio-demographic factors

Non-modifiable socio-demographic factors known to increase the risk of macro-and microvascular complications in people with diabetes include ethnicity (92, 93), increasing age (72, 75, 78, 87) and male gender (88, 94, 95).

Lower socioeconomic status (SES), measured by income, education, employment, occupation, or living in an underprivileged area, has been associated with higher rates of fatal and nonfatal CVD disease among people with diabetes (96, 97) and an increase in the risk of the developing microvascular complications (79, 83, 98-101). Lower SES is considered to influence the development of such complications through health behaviours, access to care, and processes of diabetes care (98, 101-104). For example, among people with diabetes lower educational attainment has been associated with poorer disease management, fewer ophthalmologic visits and fewer foot examinations (98).

2.8 Prevention of blindness due to diabetic retinopathy

Visual impairment and blindness due to diabetic retinopathy are preventable in the vast majority of cases, through optimal treatment of diabetes, and control of risk factors such as hypertension and hypercholesterolemia (75, 105). Evidence from clinical trials documents the benefit of early laser treatment in preventing blindness among individuals with diabetic retinopathy (106-108). However, this condition is asymptomatic until it reaches an advanced stage and sight cannot be restored once

lost to diabetic retinopathy (50). Therefore, the success of treatment is dependent on early detection and timely referral (109).

2.8.1 Screening for diabetic retinopathy

Diabetic retinopathy meets the World Health Organization (WHO) criteria for screening (110, 111). First, diabetes-associated visual impairment is an important public health problem and the natural history of diabetic retinopathy is well defined and understood. Second, diabetic retinopathy is asymptomatic until it reaches an advanced stage therefore it has a latent stage. A universally accepted and effective treatment is available (third criteria); screening detects early sight-threatening eye lesions which can be treated effectively with laser photocoagulation. Finally, retinal screening has been shown to be cost effective in terms of sight years preserved compared with no screening (112) and the risk of moderate to severe visual impairment due to diabetic retinopathy can be reduced by up to 50% (108). As a result, international policy and clinical guidelines recommend the implementation of systematic diabetic retinopathy screening programmes as part of national diabetes strategies (113, 114).

2.9 Diabetic retinopathy screening programmes

In 1989, a group of patient representatives, governmental representatives and diabetes experts met to discuss the growing problem of diabetes across Europe. Recommendations from this meeting were published in the St Vincent Declaration in 1990 (113). The declaration outlined key five year targets for diabetes, which were *'to elaborate, initiate and evaluate comprehensive programmes for detection and control of diabetes and its complications'* and to *'implement effective measures to*

reduce new blindness due to diabetes by one third or more', among other priorities relating to CVD, renal disease and amputations (113).

In response to this, representatives from 21 European countries established a protocol for the implementation of diabetic retinopathy screening in 1991 (115). The working group concluded that the cost of organising nation-wide screening was substantially lower than the costs involved in late treatment and supportive care for people who had lost their sight due to diabetic retinopathy (115). In 2005, a conference took place in Liverpool to review progress of goals that were outlined in the St Vincent's Declaration. The Liverpool Declaration reiterated the importance of screening (114) and recommended that the risk of visual impairment due to diabetic retinopathy should be reduced through *'the introduction of systematic screening programmes that will reach at least 80 % of the population with diabetes; the employment of trained professionals and personnel; and the provision of universal access to laser therapy'* (114). Since retinal screening is crucial for early detection and timely treatment, many countries have introduced population-based screening programmes as part of their national diabetes strategy (116, 117).

2.9.1 Diabetic retinopathy screening services in Ireland

In Ireland, the lack of a national population-based retinal screening programme had been highlighted as a deficit in diabetes care for over two decades (118). Screening was delivered on a limited basis by a number of local services using different models of service provision (119). In 2002, the Diabetes Service Development Group (120) outlined a proposal for the implementation of a national screening service in Ireland. Four years later, the Department of Health and Children recommended a structured diabetic retinopathy screening programme as a priority for people with diabetes. This

priority was emphasized again by the Expert Advisory Group (EAG) for Diabetes (119) in 2007; during the same year a National Retinopathy Screening committee was established to develop a strategy for the development and implementation of a national population-based retinal screening programme (121). The need for a national population-based retinopathy screening programme was highlighted again in 2010 when the National Clinical Programme for Diabetes (NCPD) was established (7). The implementation of this service was a key priority area for the NCPD given the previous groundwork of the EAG for Diabetes. In 2011, the development and implementation of a national population-based retinal screening programme was handed over to the National Screening Service (122).

2.9.2 The national diabetic retinopathy screening programme

In 2013, Diabetic Retinascreen was introduced to provide free, annual retinal screening (and where necessary, treatment) to anyone aged 12 years or older with diagnosed diabetes. The overall aim of the screening programme is to reduce the risk of sight loss among people with diabetes by the early detection and treatment of sight-threatening retinopathy (122). Implementation of Diabetic Retinascreen changed the provision of diabetic retinopathy screening in Ireland by providing universal screening access for people with diabetes, standardising the delivery of screening and improving the quality of screening (123). Estimates suggest that the programme could prevent 235 cases of blindness and 2,500 cases of visual impairment over the first 4.5 years of implementation, if universal uptake is achieved (124). This reduction in diabetes-related morbidity will benefit the individual and society by improving quality of life and by reducing the public health burden of blindness due to diabetic retinopathy (122, 123).

2.10 Uptake of retinopathy screening programmes

Although evidence shows that retinal screening is effective at detecting unrecognised sight-threatening retinopathy, the success of any screening programme depends on continued high levels of uptake; a high proportion of the target population has to be screened so enough cases of sight-threatening diabetic retinopathy can be detected and treated (125). However, unlike most other screening programmes, screening for diabetic retinopathy targets a population with a predefined illness who already face significant healthcare and self-management demands. Retinal screening is a life-long commitment for people with diabetes.

Consequently, ensuring high uptake to a retinal screening programme is challenging (116, 126) and screening rates consistently fall far below recommended levels. Internationally, non-attendance to retinopathy screening has been highlighted as an issue (71, 127-154); with non-attendance rates ranging from 24% in the USA to 44% in the UK. Within the UK, there is wide variability in screening uptake between primary care practices and regions (140). Issues with uptake have also been previously highlighted by regional screening programmes in Ireland, with non-attendance rates ranging from 20% to 51% (155-157). During the early implementation phase of Diabetic Retinascreen, programme uptake has been highlighted as a concern. In the first round of screening, of the 154,734 people invited to participate in the programme 73,201 people (47%) attended a screening appointment (17).

2.10.1 Barriers to screening attendance

Research has shown that people least likely to attend screening appointments are at greater risk of sight-threatening retinopathy because they are more likely to have

other risk factors, including poor glycaemic and blood pressure control (147, 154). Various studies have demonstrated lower attendance rates among younger adults (130, 133, 138, 142, 145, 149, 150, 154), people with type 1 diabetes (149, 150) and those with a shorter time since diabetes diagnosis (127, 130, 133, 135, 136, 150) . Social deprivation (138, 139, 142, 145, 149, 150) and relative lack of education (127, 130, 136) have also been associated with poor uptake of screening; with those from the lowest socio-economic groups being less likely to attend.

Barriers to screening attendance are multifactorial and vary in different populations and healthcare systems. For example, cultural barriers such as language have been reported in ethnically diverse populations (138, 140, 143). For those living in rural or remote locations, difficulties with access due to transportation issues are often cited as a barrier to attendance (132, 138, 140, 141, 144). In countries such as the USA (127-129, 131, 132, 148) and Australia (146), lack of health insurance and financial constraints are common barriers to screening attendance. However, some barriers to diabetic retinopathy screening attendance have been highlighted consistently in the international literature.

Common individual-level barriers include, limited awareness of diabetic retinopathy (130, 131, 136, 144, 146, 157), lowered perception of risk (127-129, 131, 132, 144, 146), psychological factors such as fear of diagnosis (137, 144), and practical barriers such as the side effects from mydriasis drops (141, 146, 157), work commitments (141, 144, 146) and competing priorities (137, 145, 148). Lewis et al. 2007 (144) carried out a qualitative study to explore influences on retinopathy screening attendance among patients and providers at three ophthalmic outpatient clinics in the UK. The study found that a lack of awareness was the greatest barrier to

attendance. However, these deficits in knowledge were quite specific as participants knew diabetes could affect the eyes but were not aware that it could lead to blindness. Additionally, a lack of awareness regarding the asymptomatic nature of diabetic retinopathy was a common barrier cited by participants. The fear of vision loss motivated screening attendance, however, the fear of being diagnosed with advanced-stage retinopathy was an important deterrent for attendance (144). Similar barriers were reported from focus groups of non-attenders to retinopathy screening carried out at a medical centre in the USA (129). Participants in this study were unaware that the late stages of diabetic retinopathy were asymptomatic and that floaters or “spots” were an important symptom of severe retinopathy (129).

Provider-level barriers have also been explored in the literature and include, inconvenient screening location (138, 148), restricted availability of appointments (132, 138, 141) and long waiting times (136, 138, 144). Moreton et al. 2017, (138) investigated provider-levels factors that influenced uptake to the English national diabetic retinopathy screening programme among patients at 79 primary care centres. The study suggested that the variation in screening uptake between practices could be partly explained by differences in the availability and flexibility of screening appointments offered by providers, the convenience of the screening location and a general interest taken by the primary care centre in diabetes care (138).

2.10.2 Facilitators of screening attendance

Factors that have been shown to positively influence uptake to retinopathy screening programmes include a fear of impaired vision (136, 144, 146), a recommendation from a healthcare provider (129, 135, 136, 146, 157), mobile screening service (138,

150) and improved communication between screening providers (137, 140). In Australia, Lake et al. 2017 (146) explored facilitators to retinopathy screening attendance among people with type 2 diabetes. The study found that the benefits of screening, such as early detection of diabetic retinopathy and feeling reassured facilitated attendance. Additionally, participants who were advised by their GP to have an eye examination, or were referred to an eye specialist for screening at diagnosis, reported initiating screening in a timely manner (146).

2.10.3 Factors influencing screening attendance in Ireland

In Ireland, there is a dearth of information on the barriers to or facilitators of screening attendance. One study carried out by Dervan et al., 2008, (157) explored factors that influenced uptake of retinopathy screening in two hospital-based diabetes clinics in Dublin. A questionnaire covering demographics, diabetic medical history and the knowledge of and attitudes to diabetic retinopathy was administered to all adults who were due to attend the diabetes clinic over a two month period (December 2001 to January 2002). Of the 209 patients with diabetes included in analysis, 169 (81%) had attended retinopathy screening in the previous 12 months. In line with existing literature, lack of knowledge regarding the need for retinopathy screening and the effect of mydriasis drops in prohibiting driving were the main barriers to attendance. A recommendation from a healthcare professional about the importance of regular retinopathy screening and an acceptance that screening was part of usual diabetes care were predictors of attendance.

2.10.4 Consequences of non-attendance

Non-attendance at diabetic retinopathy screening is costly for the individual with diabetes and the health service. People who do not attend for screening frequently

are at increased risk of sight-threatening diabetic retinopathy and the risk increases with the duration that an individual is unscreened (71). Non-attendance has major financial consequences. In the UK, it has been estimated that non-attendance costs approximately £78 000 (€97 000) over one year based on data from one primary care trust Lawrenson (158).

2.11 Summary

Diabetes is a chronic disease with serious complications and is an important public health problem. It is one of four priority non-communicable diseases targeted for action by world leaders. Globally, prevalence rates have increased rapidly over the past three decades.

Within-country estimates of the total population with diabetes and the proportion of people who have developed complications are needed to inform public health policy on care for people with diabetes. In the absence of a diabetes register, estimates of diabetes and related complications are generated from available data sources.

The systematic review (Chapter 3) compiled available epidemiological data regarding the public health burden of diabetes in Ireland. Critical assessment of the current evidence base also enabled identification of the best available data sources to use in this thesis. Data identified in the review are used to describe trends in the prevalence of diagnosed diabetes over a 17-year period (1998 to 2015) (Chapter 3). In addition, estimates of the population with diabetes were required to calculate incidence rates of visual impairment and blindness due to diabetes in the population with diabetes (Chapter 6).

Similar to other countries, Ireland is experiencing an increase in the ageing population which will inevitably result in an increase in the prevalence of chronic illness. It is important that the magnitude of diabetes and its complications is assessed within the older population in Ireland. Findings from Chapter 4 will provide robust data to plan appropriate health, medical, social and economic policies. Many determinants for macro-and microvascular complications in people with diabetes exist. The roles of clinical and socio-demographical risk factors for macro-and microvascular complications in people with diabetes are well documented but there is limited evidence in the Irish context. This deficit in knowledge is addressed in Chapter 5. Identification and treatment of risk factors can delay or prevent the development of diabetes related complications.

Rates of blindness due to diabetic retinopathy have been reported from many countries and have been published in peer-reviewed journals. In Ireland, rates of blindness due to diabetic retinopathy in the total population were calculated in 1998 and 2003, using data from the NCBI. Contemporary data is important for measuring the impact of improvements in care and for monitoring the progress of Diabetic Retinascreen (Chapter 6). Evaluation of the implementation of a public health intervention aimed to prevent diabetes related blindness (Chapter 7) is an essential first step to understanding the effectiveness of a national screening programme in the Irish health care setting.

The research in this thesis provides reliable data on the incidence prevalence of diabetes and its complications. Findings will play an important role for population health by describing the public health burden of diabetes in Ireland and providing recommendations for the on-going implementation of Diabetic Retinascreen. In

addition, this thesis will provide key source data to identify trends in diabetes and its complications at national level to facilitate diabetes program planning and to inform policy decisions including resource allocation.

3. EPIDEMIOLOGY OF DIABETES AND COMPLICATIONS AMONG ADULTS IN THE REPUBLIC OF IRELAND 1998- 2015: A SYSTEMATIC REVIEW AND META-ANALYSIS (PAPER 1)

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3.1. Abstract

Background: Accurate estimates of the burden of diabetes are essential for future planning and evaluation of services. In Ireland, there is no diabetes register and prevalence estimates vary. The aim of this review was to systematically identify and review studies reporting the prevalence of diabetes and complications among adults in Ireland between 1998 and 2015 and to examine trends in prevalence over time.

Methods: A systematic literature search was carried out using PubMed and Embase. Diabetes prevalence estimates were pooled by random-effects meta-analysis. Poisson regression was carried out using data from four nationally representative studies to calculate prevalence rates of doctor diagnosed diabetes between 1998 and 2015 and was also used to assess whether the rate of doctor diagnosed diabetes changed over time.

Results: Fifteen studies (8 diabetes prevalence and 7 complication prevalence) were eligible for inclusion. In adults aged 18 years and over, the national prevalence of doctor diagnosed diabetes significantly increased from 2.1% in 1998 to 5.2% in 2015 ($p_{\text{trend}} \leq 0.001$). The prevalence of diabetes complications ranged widely depending on study population and methodology used (6.5-25.2% retinopathy; 3.2-32.0% neuropathy; 6-9.1% nephropathy).

Conclusions: Between 1998 and 2015, there was a significant increase in the prevalence of doctor diagnosed diabetes among adults in Ireland. Trends in microvascular and macrovascular complications prevalence could not be examined due to heterogeneity between studies and the limited availability of data. Reliable baseline data are needed to monitor improvements in care over time at a national level. A comprehensive national diabetes register is urgently needed in Ireland.

3.2 Background

Diabetes is a serious global public health issue which has been described as the most challenging health problem in the 21st century (1, 2). Cases of diabetes have progressively increased worldwide; between 1980 and 2008 there was a two-fold increase in the number of adults with diabetes (160). Type 2 diabetes is the main driver of the epidemic, accounting for approximately 90% of all cases (2). The increasing burden of diabetes is driven primarily by rising levels of obesity and an ageing population (2, 30). To date there is no national surveillance programme, or national population-based survey of diabetes in Ireland. Therefore it is difficult to quantify or monitor the impact of diabetes at a national level. Estimates from the International Diabetes Federation (IDF) (2013) suggest that the prevalence of diabetes is in line with global trends. In 2000, the IDF estimated that the prevalence of diabetes was 3.2% (161), this had increase to 6.5% in 2103 (2).

Diabetes places a significant burden of care on the individual, health care professionals and the wider health system (1, 3). Individuals with diabetes are two to four times more likely to develop CVD relative to the general population and have a two- to five-fold greater risk of dying from these conditions (47, 48). Diabetes is a significant cause of blindness in adults, non-traumatic lower limb amputations and end-stage renal disease resulting in transplantation and dialysis (2).

Understanding the epidemiology of diabetes is essential to identify public health priorities. Accurate estimates of the burden of diabetes are essential for future planning and evaluation of services. While the IDF provides prevalence estimates for countries and regions, there are substantial variations in time trends as estimates are

based on imputations (162, 163). To date, estimates of diabetes prevalence in Ireland have been largely based on data from 2007 derived from SLÁN (164). Country specific prevalence rates have also been reported in the grey literature (2); however these estimates have been extrapolated using data from the UK. The Euro Diabetes Index (2014) stated that there was a lack of reliable data to monitor diabetes related complications in Ireland (13). To date, a comprehensive overview of the diabetes situation in Ireland has not been carried out. Therefore the rationale for carrying out this systematic review is to provide a comprehensive understanding of the diabetes situation in Ireland and to highlight current gaps in existing knowledge to inform future research. The aims of this review are to (1) to systematically identify and summarise studies describing the prevalence of diabetes and the most common microvascular (retinopathy, neuropathy and nephropathy) and macrovascular complications among adults in Ireland between 1998 and 2014; and (2) explore trends in diagnosed diabetes prevalence between 1998 and 2015.

3.3 Methods

This review was produced according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses (165). Key words and study eligibility criteria were determined *a priori*.

3.3.1 Search strategy

Both peer-reviewed journal articles and reports were considered for this review. A systematic literature search was carried out in PubMed and Embase databases to identify relevant studies reporting the prevalence of diabetes, microvascular or macrovascular complications among adults within the Republic of Ireland. Keywords and Medical Subject Headings (MeSH) terms included Ireland, prevalence, diabetes,

microvascular, retinopathy, neuropathy, nephropathy, macrovascular and cardiovascular disease. Keywords were combined using the AND/OR operators (Appendix 3; supplementary file 1). Titles and abstracts of the resulting literature were screened for further consideration. Reference lists of articles were also examined to identify potentially relevant studies. In addition, a Google search was conducted using the keywords prevalence, diabetes, retinopathy, neuropathy, nephropathy and Ireland to identify relevant grey literature. Searches were carried out between January 2014 and March 2014. A second search was carried out in December 2015 to ensure the review included all up to date relevant information.

3.3.2 Inclusion criteria

Studies were eligible for inclusion if they met the following criteria: (1) conducted in the Republic of Ireland between 1998 and 2014; (2) cross-sectional study design or baseline data from longitudinal studies; (3) prevalence estimates reported for adults aged ≥ 18 years, including men and women; (4) data provided on diabetes prevalence (including a self-report of a previous doctor diagnosis and undiagnosed diabetes) and/or the prevalence of microvascular complications (retinopathy, neuropathy, nephropathy) or macrovascular complications (myocardial infarction, congestive heart failure, stroke or TIA) in persons with diabetes; (5) if prevalence data were not reported, sufficient detail to calculate the numerator and denominator was provided; (6) the total sample size was ≥ 200 ; (7) adequate information was reported on the methods used.

3.3.3 Exclusion criteria

Studies containing participants from Northern Ireland, restricted to a specific sub-population (including hospital-based studies), solely focused on Type 1 diabetes, pre-

diabetes or gestational diabetes were excluded from this review. Model estimates of prevalence were also excluded. If multiple articles provided information on a single study, the article detailing the most comprehensive data was selected. Full text articles were retrieved for all potentially eligible studies and were independently reviewed by three authors (MT, MG, and KO'N).

3.3.4 Data abstraction and quality assessment

For each eligible study, three reviewers (MT, MG, and KON) individually collected relevant information using a structured data extraction form. The methodological quality of each included study was assessed using a critical appraisal checklist for studies used in systematic reviews addressing questions of prevalence (166). This appraisal tool was developed to specifically examine the internal and external validity of prevalence data included in systematic reviews. Methodological quality was considered 'low' if three or fewer criteria were met, 'moderate' if four to six criteria were met and 'high' if seven to nine criteria were met. Articles were not excluded on the basis of quality. Any inconsistencies in data abstraction and quality assessment between reviewers were resolved through consensus.

3.3.5 Statistical analysis

A meta-analysis was carried out using STATA version 13.1 (StataCorp, College Station, TX, USA). Studies were grouped into four categories: diagnosed diabetes among adults aged 18+ years; diagnosed and undiagnosed diabetes among adults aged 45+ years; diagnosed diabetes among adults aged 45+ years; undiagnosed diabetes among adults aged 45+ years. Pooled estimates of diabetes prevalence and 95% confidence intervals (95% CI) were calculated. Trends in pooled prevalence could not be explored as there was a lack of available data from different time points; therefore

an overall estimate was provided for each group. Heterogeneity between studies was assessed by the Chi-square based Q test and I^2 statistic. Potential publication bias was evaluated by the Egger's test. A two-tailed $p < 0.05$ was regarded to be statistically significant. High heterogeneity was found among studies reporting diabetes prevalence ($I^2 \geq 75\%$, p -value < 0.01) hence, pooled estimates were calculated using random-effects model using the method of DerSimonian and Laird (167). The results from the meta-analysis were presented in a forest plot. To determine the robustness of the results, a sensitivity analysis, based on high quality studies, was carried out. A meta-analysis of the prevalence of diabetes complications was inappropriate; factors which influence prevalence estimates (e.g. time since diabetes diagnosis, type of diabetes, method of diagnosis) either varied between studies or were not reported. Instead a narrative synthesis provides a summary of relevant data.

3.3.5.1 Trends in diagnosed diabetes

As trends in diabetes prevalence could not be calculated by meta-analysis, original datasets from four national population based studies (16-19), identified during the literature search were obtained and analysed. In each dataset, diabetes was defined by a self-report of a previous doctor diagnosis. A detailed description on study methodology can be found elsewhere (18, 168). Using data from these national surveys, multivariate Poisson regression models were undertaken to impute annual gender and age-specific (18-39 years, 40-69 years, ≥ 70 years) rates of diagnosed diabetes and to assess trends over time. The dependent variable was the number of cases of diagnosed diabetes and the exposure variables were year of data collection and age group. An interaction term between calendar year and age group was

considered to explore whether the rates of change over time differed across age groups; a non-significant interaction indicated a common linear trend in prevalence. The predict command was used post analysis to calculate the expected rates of diagnosed diabetes for each calendar year of the study. The gender and age-specific predicted rates were applied to 2004–2015 population data so the absolute number of diabetes cases could be obtained. Annual population estimates were obtained from the Central Statistics Office (CSO), Ireland (30). A census took place in Ireland in 2002, 2006 and 2011; data for other study years were CSO inter-censal estimates (30). Prevalence was calculated by dividing the number of expected cases of doctor diagnosis of diabetes by the total study population and was expressed as a percentage with 95% CI. Prevalence estimates were presented graphically in Excel.

3.4 Results

3.4.1 Study selection

Results of the literature search and the selection process are summarised in Figure 3. One report (169) provided two estimates for diabetes prevalence from two separate studies (16, 17). In total, 15 studies were eligible for inclusion; 8 reporting estimates on diabetes prevalence and 7 reporting estimates on complication prevalence. Of the included studies, the methodological quality was considered moderate in nine studies and high in the remaining studies (Appendix 3; supplementary file 2).

3.4.2 Characteristics of selected studies

Characteristics of studies that reported the prevalence of diabetes or diabetes complications are presented in Table 3 and Table 4. In all included studies, data collection were carried out between 1998 and 2011. Studies varied in terms of the study design, setting (national vs. regional), sampling approach and study quality. Of

the 8 studies reporting on diabetes prevalence, five articles had been published in peer-reviewed journals (164, 170-173), while three estimates were reported in two national reports (169, 174). Of the 7 studies reporting diabetes complications, six had been published in peer-reviewed journals (14, 175-179), while one audit (180) provided data on the prevalence of diabetes related complications. Five studies utilised an objective data source to ascertain the prevalence of complications (14, 175, 176, 179, 180). The diagnostic criteria for complications was unclear in three studies (177, 178, 180) whereas the remaining four used validated diagnostic criteria to identify cases (14, 175, 176, 179), however these criteria differed between studies reporting on the same complication.

3.4.3 Prevalence of diabetes in included studies

Table 5 reports the prevalence of diabetes by study. Individual and summary estimates, based on a random-effects meta-analysis are illustrated in Figure 4. There was significant heterogeneity in all groups. Sensitivity analysis only showed lower heterogeneity in combined prevalence rates for undiagnosed and diagnosed diabetes among adults aged over 45 years ($I^2 \geq 25\%$, $p=0.36$); with a pooled prevalence of 9.2% (95% CI: 8.6-9.8) (Appendix 3; supplementary file 3). According to the Egger's test, there was no evidence of publication bias ($p=0.27$).

3.4.4 Trends in the prevalence of diagnosed diabetes over time

In adults aged 18 years and over, the prevalence of diagnosed diabetes increased from 2.2% (95% CI: 1.7%-2.7%) in 1998 to 5.2% (95% CI: 5.1%-5.3%) in 2015 ($p_{\text{trend}} < 0.001$); representing an absolute mean increase of 0.17% per year. In 2015, the incidence of diagnosed diabetes was 0.2/100 population.

Figure 5 illustrates the age-specific prevalence of self-reported diagnosed diabetes from 1998 to 2015. In adults aged between 18 and 39 years, the prevalence of self-reported doctor diagnosed diabetes remained stable between 1998 and 2015 in both men and women; $p_{\text{trend}} > 0.05$. However, there was a significant increase in prevalence among men aged 40 to 69 years between 1998 (3.5% [95% CI: 3.4%-3.6%]) and 2015 (6.6% [95% CI: 6.5%-6.7%]; $p_{\text{trend}} < 0.001$). The prevalence of diabetes also increased among women in the same age group over the same time period (1998- 2.5% [95% CI: 2.4%-2.5%] to 2015-4.2% [95% CI: 4.1%- 4.3%]; $p_{\text{trend}} < 0.001$). In those aged 70 years and over, an upward trend in prevalence among both men (1998- 8.2% [95% CI: 8.0%-8.3%] to 2015-15.1% [95% CI: 14.8%-15.2%]) and women (1998- 4.7% [95% CI: 4.5%- 4.8%] to 2015- 10.7% [95% CI: 10.5%- 10.8%]) was also observed; $p_{\text{trend}} < 0.001$.

3.4.5 Prevalence of microvascular and macrovascular complications

Table 6 describes the prevalence of microvascular and macrovascular complications in each included study. Five out of seven studies reported the prevalence of retinopathy (175, 177-180). Among people with type 2 diabetes, a population based study reported the prevalence of diabetic retinopathy to be 8.5% in 2009-2011 (178); a regional study, carried out among primary care patients, found a higher prevalence of 24.8% (179); however this estimate included patients with Type 1 and 2 diabetes and was based on objective data. A similar estimate (25.6%) was reported in a comparable cohort of primary care patients in a different region (180).

In terms of diabetes-related neuropathy, a divergence in the reported prevalence between studies was also observed. Data from 12 primary care centres in the West of Ireland indicated a prevalence of past documented neuropathy to be 3% (176). On

the other hand, a population-based study reported a prevalence of 14.6% (178). These patients had similar average duration since diagnosis (5.0 years (178) vs. 7.8 years (176)); however, the latter estimate was based on self-reported data. Prevalence rates for leg amputations were 1.7% among primary care patients with diabetes (180). In contrast, the prevalence of non-traumatic lower leg amputation was lower (0.2%) in a population-based study which utilised national hospital discharge data (14).

With reference to nephropathy, prevalence among those with type 2 diabetes was similar in two studies (177, 178). In the three studies presenting data on macrovascular complications, a marked difference in prevalence was observed. A primary care audit reported a prevalence of 3.5% in patients with Type 1 and 2 diabetes (180). In contrast, among those with type 2 diabetes, a population based study reported a higher prevalence of 15.1% (178).

3.5 Discussion

3.5.1 Main findings

This systematic review is the first study to compile all available evidence reporting the prevalence of diabetes (diagnosed and undiagnosed) and related complications (microvascular and macrovascular) among adults in Ireland between 1998 and 2015. Fifteen studies (eight describing diabetes prevalence and seven describing complication prevalence) were included.

Similar to other systematic reviews (38, 181, 182); comparability between studies was limited due to differences in study population, sampling methods and diagnostic criteria. Additionally, substantial statistical heterogeneity was detected between studies reporting the prevalence of diabetes; therefore our pooled estimates have to

be interpreted with caution. Sensitivity analysis, based on study quality, lowered the heterogeneity of combined prevalence rates for undiagnosed and diagnosed diabetes among adults aged over 45 years. However, this may reflect variability between prevalence estimates rather than study quality. Trends in diabetes prevalence could not be explored by meta-analysis, therefore, original data from four population-based national studies (16-19) were obtained to explore time trends in doctor diagnosed diabetes prevalence between 1998 and 2015. Over a seventeen year period, we observed an important increase in the national prevalence of self-reported diagnosed diabetes in Ireland.

Consistent with previous research (183-185) trends in the prevalence of self-reported diagnosed diabetes remained constant in adults aged 18 to 39 years, while an increasing prevalence was observed in the older age groups. We were unable to distinguish between the various types of diabetes in this review; however it can be assumed that type 2 diabetes is driving the increase in prevalence as it accounts for 90% of all diabetes cases (1, 2). The prevalence of diabetes was consistently higher in males compared to females. Evidence suggests that men are at a higher risk of developing type 2 diabetes as they develop diabetes at a lower BMI, are more predisposed to central fat deposition and are more prone to insulin resistance (186). Therefore, men are more like to develop type 2 diabetes in response to increasing levels of obesity (187). On the other hand, the higher prevalence in the male population may reflect preferences in diagnostic methods. Evidence has highlighted that the prevalence of FPG diagnosed diabetes is higher among men, whereas women are more commonly diagnosed by a 2-hour plasma glucose test (188). While it is not possible to determine the method of diabetes diagnosis in this review; it is

important to consider how these gender differences may influence diagnosed diabetes prevalence estimates over time.

Similar to diagnosed diabetes, trends in the prevalence of undiagnosed diabetes could not be explored by meta-analysis as only two nationally representative studies had relevant data (164, 189). The prevalence of undiagnosed diabetes, based on HbA1c, decreased from 2.8% in 2007 to 0.9% in 2009-2011 among adults aged ≥ 45 years and ≥ 50 years, respectively. While the prevalence of diagnosed diabetes increased from 6.1% in 2007 (164) to 8.6% in 2009-2011 (172). This shift from undiagnosed to diagnosed diabetes prevalence has also been observed in a study carried out in Germany (163). This decrease in undiagnosed diabetes prevalence may be attributable to earlier detection of diabetes (163). In Ireland, screening high risk patients for type 2 diabetes has been encouraged since the introduction of national guidelines for diabetes-care in 2002 (120). Another study based on 29144 adults aged 45-75 years with private health insurance, reported the prevalence of undiagnosed diabetes to be 1.8% in 2009-2012 (190) . However this estimate was derived from FPG; evidence suggests that HbA1c criteria may underestimate prevalence compared with estimates using FPG (183, 188, 191).

The prevalence of diabetes complications varied substantially between studies therefore comparisons between studies have to be interpreted with caution. These variations may be attributable to differences in disease duration, study setting (primary care vs. population- based) or heterogeneity in the criteria used to diagnose macrovascular and microvascular complications. Objective data describing the national prevalence of diabetic retinopathy was not available however, regional data on diabetic retinopathy showed that approximately 25% of primary care patients had

been diagnosed with this condition (179, 180). This estimate is higher than a previous hospital-based study based on patients with type 2 diabetes (14.8%) (192) and primary care data from the UK (19.6%) (63) but lower than global prevalence estimates (34.6%) (6). Though, caution has to be applied when interpreting the results as both regional studies included in this review reported a low uptake rate of retinopathy screening at approximately 50% (63, 179). Additionally, characteristics between attenders and non-attenders were not compared in either study; hence it is possible that there were systematic differences between the two groups. Healthier people are more likely to participate in research; therefore the prevalence of diabetic retinopathy may have been underestimated. As a national screening programme for diabetic retinopathy was introduced in 2013 (122), future estimates based on this national programme may be more reliable.

3.5.2 Strengths and limitations

The strengths and limitations of this systematic review should be noted. Both peer-reviewed articles and estimates detailed in the grey literature were included to limit the impact of publication bias. Original data from four national studies were obtained so trends in diagnosed diabetes prevalence could be examined over a 17 year period. Although response rates were below the optimal rate of 70%, the representativeness of each study has been demonstrated previously (18, 193), so it can be assumed that the results presented can be generalised to the Irish population.

However, several limitations need to be acknowledged. Firstly, studies included in this review were of moderate to high quality; however, six of the included studies relied on self-reporting to determine the prevalence of diagnosed diabetes and one study relied on self-reporting to determine the prevalence of diabetes related

complications. This approach is prone to misclassification bias which can result in an inaccurate estimation of prevalence (194). When compared to medical records, data from self-report have been shown to underestimate the prevalence of diabetic retinopathy (195). However, moderate to high levels of agreement between diabetes prevalence and self-report have been shown in several studies (196-198) . Although only data on self-reported diabetes were available, results from trend analysis are in line with other developed countries. Secondly, without the inclusion of undiagnosed diabetes in our trend analysis, we acknowledge that diabetes prevalence is underestimated. Finally, significant increases in diagnosed diabetes prevalence were observed over time but these increases may be attributed to heightened awareness among patients, changes in clinical practices including increases in screening for type 2 diabetes and better survival rates for patients with diabetes (199). However, there is a lack of data on mortality rates among people with diabetes in Ireland; therefore it is not possible to determine whether our increasing trends in prevalence are due to improved health outcomes in those with diabetes.

3.5.3 Conclusions

This review provides the first comprehensive overview of the burden of diabetes in Ireland. In the absence of a national diabetes register, the findings in this review provide a robust estimate of the trends in prevalence of doctor diagnosed diabetes among the adult population in Ireland. Findings from this review are in accordance with the Euro Diabetes Index (2014) (13); there is a lack of information relating to the prevalence of undiagnosed diabetes, macrovascular and microvascular complications. Interpretation of available data was limited due to inconsistencies in reporting, limited availability of objective data and standardisation in diagnostic

criteria. We suggest that the true burden of diabetes in Ireland is underestimated (200). In 2010, the National Clinical Programme in Diabetes was established to improve and standardise patient care in Ireland (7). Reliable baseline data are needed to monitor improvements in care over time at a national level. Therefore, we suggest that a comprehensive national diabetes register is urgently needed in Ireland.

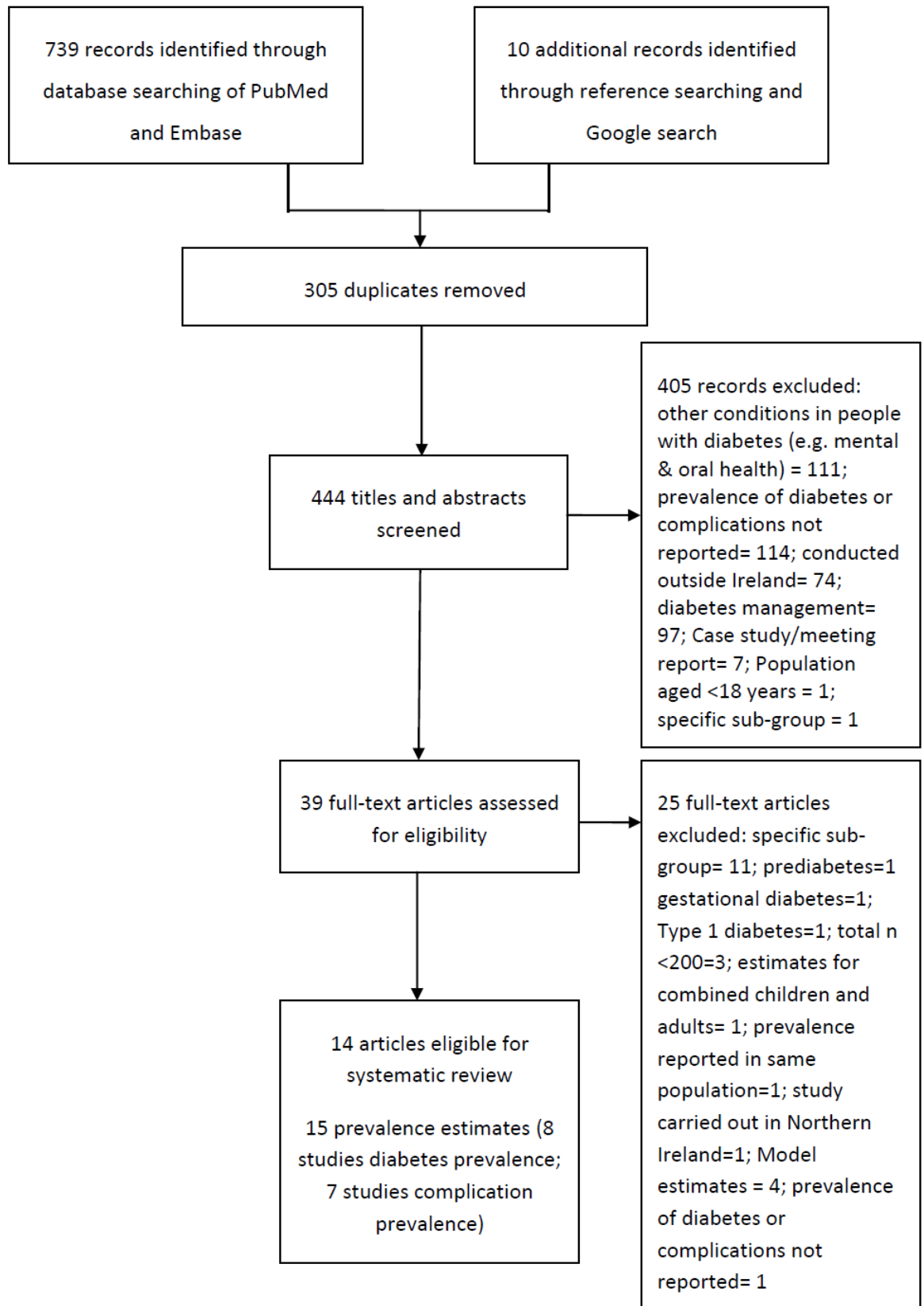


Figure 3. PRISMA flow chart depicting the selection process of articles included in the systematic review

Table 3. Characteristics of studies reporting the prevalence of diabetes among adults in the Republic of Ireland, 1998-2011

Author	Year of data collection	Study design	National or regional	Setting	Population	Sampling frame	Sampling method	Sample size	Males (%)	Age (years)	Study quality (out of 9)
Diabetes prevalence											
Sheily and Kelleher ²¹	1998	Cross-sectional	National	Household	General population	Electoral register	Multistage sample	1632	47.7	≥ 55	7
Creagh <i>et al.</i> ²²	1998	Cross-sectional	Regional	17 GP practices	Primary Care Patients	Practice list	Stratified random	1018	48.2	50-69	6
Census Statistic Office (CSO) ²⁶	2001	Survey	National	Household	General population	Census	Total sample	3917203	-	≥18	5
Sheily and Kelleher ²¹	2002	Cross-sectional	National	Household	General population	Electoral register	Multistage sample	1745	41.7	≥ 55	7
Balanda <i>et al.</i> ¹¹	2007	Cross-sectional	National	Household	General population	Geodirectory	Multistage probability	10,364	49.5	≥18	8
Gallagher <i>et al.</i> ²³	2009-2010	Cross-sectional	National	Database	Patients covered by GMS, LTI, DPS schemes	HSE-PCRS pharmacy claims data base	Total sample 2009 2010	3493974 3490877	-	≥16	6
Leahy <i>et al.</i> ²⁴	2009-2011	Cross-sectional analysis of longitudinal study	National	Household & designated health centre	General population	Geodirectory	Multi-stage probability	5377	46.5	≥50	8
O'Connor <i>et al.</i> ²⁵	2010-2011	Cross-sectional	Regional	Primary care centre	Patients	Practice list	Random	2047	49.2	50-69	8

Table 4. Characteristics of studies reporting the prevalence of diabetes related complications among adults in the Republic of Ireland, 1998-2011

Author	Year of data collection	Study design	National or regional	Setting	Population	Sampling frame	Sampling method	Sample size	Males (%)	Age (years)	Study quality (out of 9)
Complication prevalence											
Kelliher <i>et al.</i> ²⁷	2003	Cross-sectional	National	National Council for Blind Ireland (NCBI)	All person registered blind	NCBI database	Total sample	6826	-	Adults	8
Buckley <i>et al.</i> ³²	2009	Cross-sectional	National	Population	People with diabetes	Hospital In-Patient Enquiry (HIPE) dataset	Total sample	723551	-	≥20 years	9
Marsden <i>et al.</i> ³³	2008-2009	Audit	Regional	20 general practices	Patients with T1 & T2 DM registered with diabetes structure care programme	Practice patient list	Every second person from list	1071	51.9	63 (sd 13)	5
Hurley <i>et al.</i> ²⁸	2008-2009	Cross-sectional analysis of longitudinal study	Regional	General practices with diabetes nurse	Patients with T1 & T2 DM	Practice diabetes register	Researchers selected eligible participants	563	60	64 (sd 13.4)	6
Farrell & Moran ²⁹	2010	Cross-sectional	Regional	30 general practices	T2 DM	Diabetes imitative database	Stratified sampling	309	-	-	5
Tracey <i>et al.</i> ³⁰	2009-2011	Cross-sectional analysis of longitudinal study	National	Household	General population	Geodirectory	Multi-stage probability	8175	53	≥50	8
McHugh <i>et al.</i> ³¹	2011	Cross-sectional	Regional	30 general practices	Patients with T1 & T2 DM	Practice patient list	All persons with T1&T2DM invited	1542	57.3	65 (sd 13)	7

Table 5. Prevalence of diabetes among adults in included studies, 1998-2011

Study	Year of data collection	Response rate (%)	Sample size	Age	Diabetes type	Diagnostic criteria	Estimate	Prevalence % (95%CI)		
								Males	Females	Total
Sheily and Kelleher ²¹	1998	62	1632	≥ 55 years	All	SR*	Diagnosed	6.1	4.3	5.4
Creagh <i>et al</i> ²²	1998	69.1	1018	50-69 years	2	FPG^	Diagnosed	-	-	2.8
							Undiagnosed	-	-	1.2
							Total	-	-	3.9 (2.9-5.4)
							Total ≥65 years	13	7	-
CSO ²⁶	July- Sept. 2001	-	3917203	≥ 18 years	All	SR	Diagnosed ≥18 years	-	-	1.5
							≥65 years	1.7	1.4	4.5
								8.0	5.1	6.4
Sheily and Kelleher ²¹	2002	53	1745	≥ 55 years	All	SR	Diagnosed			
Balanda <i>et al.</i> ¹¹	2007	62	10,364	≥ 18 years	All	SR or medication use or HbA1c [#]	Diagnosed	-	-	0.7 (0.5 - 0.9)
							18 - 44 years	-	-	6.1 (5.5-6.9)
							45+ years	6.8 (5.7-7.9)	5.4 (4.3-6.6)	3.5 (3.1-3.9)
							Total ≥ 18 years	-	-	2.8 (1.4-4.1)
							Undiagnosed (≥ 45 years)	4.0 (1.6-6.3)	1.7 (0.3-3.0)	
							Total (diagnosed & undiagnosed ≥ 45 years)	10.8 (8.2-13.4)	7.1 (5.3-8.9)	8.9 (7.3-10.5)
Gallagher <i>et al.</i> ²³	2009 2010	-	3493974 3490877	≥ 18 years	2	At least 1 prescription of diabetes medication	Diagnosed	-	-	2.8
							2009 2010	- -	- -	3.1
Leahy <i>et al.</i> ²⁴	2009-2011	62	5377	≥ 50 years	2	SR or medication use or HbA1c [#]	Diagnosed	-	-	8.6 (7.6-9.5)
							Undiagnosed	-	-	0.9 (0.6-1.1)
							Total (diagnosed & undiagnosed)	11.8 (10.3-13.3)*	7.3 (6.0-8.5)*	9.5 (8.5-10.4)
							50-59 years	5.1 (4.0-7.0)	4.0 (5.0 (4.0-6.0)
							60-69 years	6.0 (5.0-8.0)	14.0 (11.0-16.0)	-
							70-79 years	12.0 (8.0-14.0)	17.0 (14.0-21.0)	-
							80+ years	10.0 (5.0-15.0)	25.0 (15.0-36.0)	16.0 (10.7-21.4)
O Connor <i>et al.</i> ²⁵	2010-2011	67.9	2047	50-69 years	2	SR or medication use or HbA1c [#]	Diagnosed	6.8*	3.1*	5.0 (4.1–6.0)
							Undiagnosed	7.1*	2.7*	3.5 (2.8–4.4)
							Total	11.1*	6.0*	8.5 (7.4–8.8)

*SR: self-reported data; ^Fasting plasma glucose (American Diabetes Association criteria (ADA, 1997); # HbA1c (ADA, 2010); *p for difference < 0.05

Table 6. Prevalence of microvascular and macrovascular complications in included studies, 2003-2011

Author	Year of study	Response rate (%)	Sample size	Age	Diabetes type	Time since diabetes diagnosis	Data source	Diagnostic method	Type of complication	Prevalence (%)
										Total
Kelliher <i>et al.</i> ²⁷	2003	-	6826	Adults	All	-	National blind registry	Visual acuity of <6/60 in better eye/ visual field subtending angle of 20 degrees/< less	Blindness due to diabetic retinopathy	4.7
Buckley <i>et al.</i> ³²	2009	-	723, 551	≥20 years	All	-	Hospital discharge data	ICD-10 codes	Non-traumatic lower leg amputation	0.2
Marsden <i>et al.</i> ²⁶	Nov 2008- March 2009	72	1071	63 years (sd 13)	T1:7.5% T2:92.3%	15 years	Electronic & paper clinical notes & referral letters	- Risk classification score ACR 2.5-25 ACR >25 - - - -	Diabetic retinopathy Foot ulcer Microalbuminuria Proteinuria Myocardial Infarction Heart Failure Transient Ischemic Attack Stroke	24.8 2.5 32.1 6.0 0.4 0.3 1.5 0.5
Hurley <i>et al.</i> ²⁸	Feb 2008- Sept 2009	68	563	64 years (sd 13.4)	T1:10% T2: 90%	7.7(8.2) years	Clinical foot examination & practice medical records	Scottish Intercollegiate Guidelines Network risk stratification system & previous doctor diagnosis	Total macrovascular Documented diabetic neuropathy Foot ulceration Past amputation Neuropathy symptoms at examination	3.5 3.0 3.7 1.7 32
Farrell & Moran ²⁹	2010	-	309	-	T2	-	Chart review	-	Diabetic retinopathy Neuropathy Peripheral vascular disease Chronic kidney disease Cerebrovascular disease	6.5 12.3 12.9 5.5 5.2
Tracey <i>et al.</i> ³⁰	2009-2011	62	655	≥50 years	T2	5 (IQR 3-10) years	SR previous doctor diagnosis	-	Diabetic retinopathy Neuropathy Leg ulcer Nephropathy Proteinuria Total macrovascular	8.2 (6-10) 14.6 (11-18) 4.2 (2-6) 5.1 (3-7) 6.1(4-8) 15.1 (12-18)
McHugh <i>et al.</i> ³¹	2011	GP= 94%; Screening uptake= 43%	1542	65 years (sd 13)	T1:4.9% T2:85.6%	-	Eye examination & clinical records	Fundus 45° digital PASA-approved camera	Background (R1) Pre proliferative (R2) Proliferative (R3) Any diabetic retinopathy	21.5 (19-23) 3.4 (2-4) 0.7 (0.4-1.3) 25.6 (23-27)

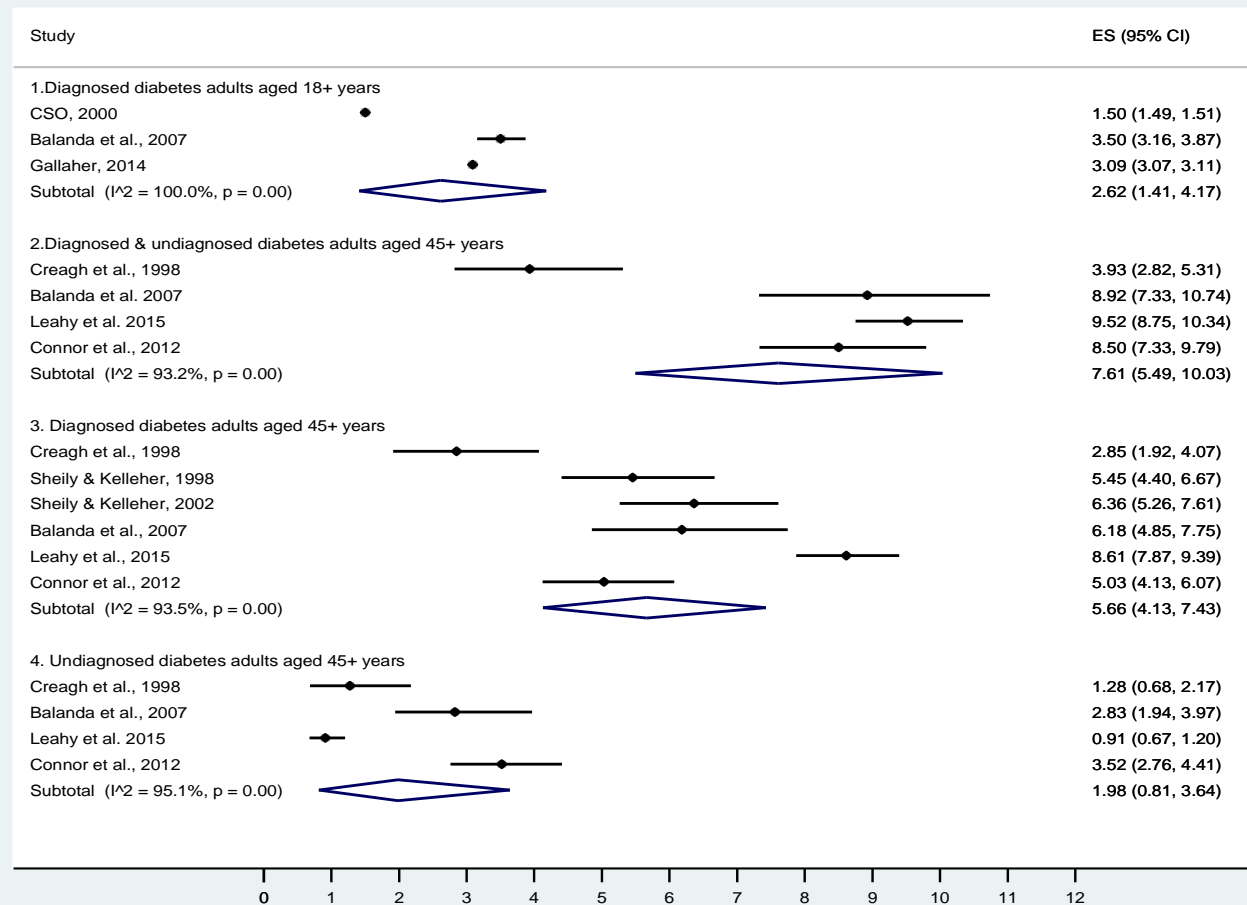


Figure 4. Forest plot of individual and summary diabetes prevalence estimates of included studies.

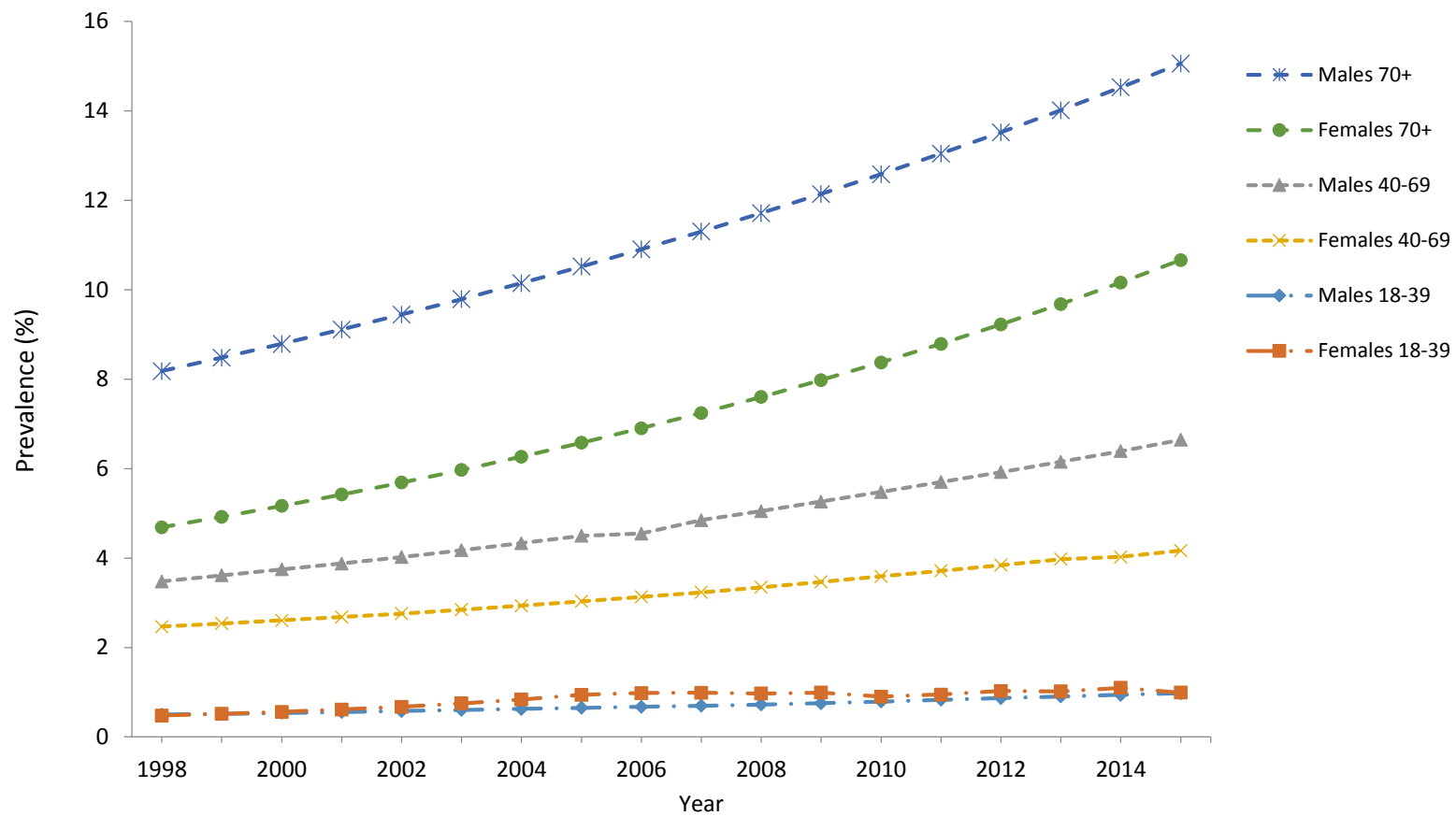


Figure 5. Prevalence of self-reported diabetes among adults aged 18 years and over in Ireland, 2004-2015.

4. THE PREVALENCE OF TYPE 2 DIABETES AND RELATED COMPLICATIONS IN A NATIONALLY REPRESENTATIVE SAMPLE OF ADULTS AGED 50 AND OVER IN THE REPUBLIC OF IRELAND (PAPER 2)

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4.1 Abstract

Aim: To investigate the prevalence of diagnosed type 2 diabetes and its related complications in a nationally representative sample of older adults in the Republic of Ireland.

Research Design and Methods: Cross-sectional analysis of a population-based sample of adults aged ≥ 50 years from the first wave of The Irish Longitudinal Study on Ageing (TILDA), (2009-2011). Diagnosed type 2 diabetes prevalence was estimated by self-report or use of oral hypoglycemic agents. The prevalence of microvascular and macrovascular complications was determined by self-report.

Results: Diagnosed type 2 diabetes prevalence was 8.4% (95% CI: 7.8%- 9.0%) and was higher among men (10.3% [95% CI: 9.4%-11.2%]) than women (6.6% [95% CI: 5.9%-7.5%]); $p \leq 0.001$. Among participants with diagnosed type 2 diabetes, the overall prevalence of microvascular complications was 26.0% (95% CI: 22.4%-30.0%) with no evidence of gender-specific differences ($p= 0.7$). The overall prevalence of macrovascular complications was 15.1% (95% CI: 12.2%-18.4%) and was higher among men (17.8% [95% CI: 14.3%-23.1%]) than women (11.4% [95% CI: 7.7%-16.4%]); $p \leq 0.001$.

Conclusions: In the absence of a national diabetes register, these findings provide a robust estimate of the national prevalence of diagnosed type 2 diabetes and level of complications among adults aged 50 years and over in Ireland.

4.2 Background

Over the past number of years, the global prevalence of type 2 diabetes has continued to rise (160, 201). Regional data from Ireland showed that the prevalence of diagnosed type 2 diabetes among middle aged primary care patients ranged from 2.8% in 1998 (170) to 5% in 2010-2011 (173). Cross-sectional analysis of a national prescription database demonstrated a higher prevalence (9.1%) among adults aged over 65 years in 2010 (202). Type 2 diabetes is a significant cause of blindness, non-traumatic lower limb amputations, end-stage renal disease and CVD (160, 201). The Cost of Diabetes in Ireland Study (CODEIRE), based on data from four hospitals in 1999/2000, found that microvascular complications were evident in 20% of patients with type 2 diabetes and macrovascular complications were present in 18% (192).

Similar to other countries, Ireland does not have a national diabetes register or universal data-capture system to monitor the burden of type 2 diabetes and related complications. Prevalence estimates rely on data from observational studies (164, 170, 173, 192, 202, 203). However, these estimates can vary due to differences in age ranges, study populations and case finding methods; comparability between studies is limited making it difficult to observe trends over time (159).

Reliable population-based data are necessary so the effectiveness of national diabetes strategies can be assessed over time (72, 159). The development of a national strategy falls under the remit of the National Clinical Programme in Diabetes, which was established in 2010 to improve and standardise care for people with diabetes in Ireland (7). Prior to the implementation of new prevention and treatment strategies for diabetes, it is important to quantify the burden of disease in the community (159). The aims of this study are to estimate the prevalence of

diagnosed type 2 diabetes among adults aged 50 years and over and to determine the prevalence of microvascular and macrovascular complications in those with diagnosed type 2 diabetes.

4.3 Methods

Data from the first wave (2009-2011) of The Irish Longitudinal Study on Ageing (TILDA) were utilised to conduct cross-sectional analysis. TILDA is a population-based prospective cohort study of community-dwelling adults aged 50 years and over; methods have been reported in detail previously (19, 193). Data collected within TILDA include computer-assisted personal interviewing (CAPI) and a health assessment. The CAPI was administered by trained social interviewers in participants' homes. Those who completed the CAPI were invited to attend a designated health assessment centre or a home-based assessment for a physical examination (19, 193). Data collected via the CAPI and during the health assessment were used in analysis. Ethical approval was obtained from the Faculty of Health Sciences Research Ethics Committee of Trinity College Dublin.

4.3.1 Classification of diagnosed Type 2 diabetes

Individuals were classified as having diabetes if they self-reported a previous doctor diagnosis or if they reported use of oral hypoglycemic agents (OHA) during the CAPI. Anyone aged <40 years at diabetes diagnosis and injecting insulin but not on OHA was classified as having Type 1 diabetes. All others who reported a doctor diagnosis of diabetes were classified as having type 2 diabetes.

4.3.2 Classification of macrovascular and microvascular complications

All participants were asked the question "Has a doctor ever told you that you have any of the conditions on this card?". Heart attack (Myocardial infarction), heart

failure (congestive cardiac failure), stroke (Cerebrovascular accident) and mini stroke (TIA) were included in the list and were defined as macrovascular complications. Participants who reported a doctor diagnosis of diabetes during the CAPI were asked the question “Has a doctor ever told you that you have any of the following conditions related to your diabetes?”. The conditions listed were: leg ulcer, protein in urine (proteinuria), lack of feeling and tingling pain in legs and feet due to nerve damage (diabetic neuropathy), damage to the back of your eye (diabetic retinopathy) or damage to your kidneys (diabetic nephropathy) and these were defined as microvascular complications.

4.3.3 Statistical analysis

Analysis was carried out in Stata version 13 for windows (StataCorp, College Station, TX) using the survey function (svy). Statistical significance was defined as $p < 0.05$. Comparisons with data from the Quarterly National Household Survey (174) demonstrated that individuals with lower levels of educational attainment were significantly under-represented in TILDA and there were also significant differences in the response rate among particular age and gender groups (19). For instance, compared to the QNHS, younger males and older females from the lower educational groups were significantly less likely to participate in TILDA. Inverse probability weights were calculated to allow for this differential non-response and were applied to all analyses to provide population estimates (19, 193).

The prevalence of diagnosed type 2 diabetes was calculated as follows: the number of TILDA participants classified with diagnosed type 2 diabetes was divided by the total TILDA population. The prevalence of macro- and microvascular complications were calculated in those with self-reported diagnosed type 2 diabetes. Prevalence

was expressed as a percentage with corresponding 95% confidence intervals (95% CI). Group-specific differences were analysed using Pearson's chi-square test for categorical data and Student's t-test for continuous data.

4.4 Results

4.4.1 Prevalence of diagnosed type 2 diabetes

A total of 8175 participants from 6282 households were recruited and completed the CAPI (response rate 62%). Overall, 672 individuals had diagnosed diabetes. Of these, 655 participants were classified as having type 2 diabetes and 17 were classified as having Type 1 diabetes. Individuals that self-reported a previous diagnosis of type 2 diabetes (n=617) did not significantly differ from those categorised as having diabetes based on use of oral hypoglycaemic agents (n=38) in terms of age (p= 0.8), gender (p= 0.3), educational attainment (p= 0.2) or cognitive function (p= 0.5). Physical measurements (Body mass index [BMI], mean waist circumference [WC], mean systolic and diastolic blood pressure) were only available for participants who attended the health assessment. (n=5864; response rate 72%).

Baseline characteristics by diagnosed type 2 diabetes status are illustrated in Table 7. The prevalence of diagnosed type 2 diabetes among TILDA participants aged ≥ 50 years was 8.4% (95% CI: 7.8%- 9.0%) and was highest in those aged 75 years and over (75+ years: 11.8% [9.9%-13.8%] vs. 65-74 years: 11.1% [9.8%- 12.4] vs. 50-64 years: 6.3% [5.6%-7.0%]). The prevalence was significantly higher among men (10.3% [95% CI: 9.4%-11.2%]) compared to women (6.6% [95% CI: 5.9%-7.5%]; $p \leq 0.001$).

4.4.2 Prevalence of diabetes-related complications

Among those with diagnosed type 2 diabetes, the overall prevalence of macrovascular complications was 15.1% (12.2%-18.4%) and was higher among men

(17.8% [14.3%-23.1%]) than women (11.4% [7.7%-16.4]); $p \leq 0.001$. The overall prevalence of microvascular complications was 26.0% [22.5%- 29.9%]; with no gender-specific differences in prevalence identified ($p=0.7$). Neuropathy was the most commonly reported microvascular complication (14.6% [11.4%-18.2%]) followed by retinopathy (8.2% [6.2%-10.9%]), proteinuria (6.1% [4.3%-8.6%]), kidney damage (5.1% [3.4%-7.6%]) and leg ulcer (4.2% [2.8%-6.4%]).

4.5 Discussion

4.5.1 Main findings

This is the first study of the prevalence of macrovascular and microvascular complications among older adults with diagnosed type 2 diabetes using nationally representative data from Ireland. Direct comparisons with research in Ireland is limited as previous studies focus on specific age groups (170, 173, 202) and/or were carried out in a specific region (170, 173, 192) or care setting (170, 173, 192) or used different case finding methods (192, 202). O Connor et al. (173) also used self-report and the use of OHAs to determine the prevalence of diagnosed type 2 diabetes in primary care patients aged 50-69 years. Yet they reported a slightly lower prevalence (5%) than in a similar age group in our study (6.3%). Likewise, O'Shea et al. (202) also reported a lower national prevalence of diagnosed type 2 diabetes in adults aged 65 years and over (9.7% vs. 11%). In contrast to our study, their estimates were based on patients who were pharmacologically treated for type 2 diabetes and did not capture those who managed their diabetes with diet alone (202). Similar to our findings, CODEIRE (192) found that among patients with type 2 diabetes from four out-patient clinics in Ireland, neuropathy and retinopathy were the most prevalent microvascular complications. However, in our study, the prevalence of these

conditions was much lower than that reported by CODEIRE (192) (neuropathy: 15% vs. 25%; retinopathy: 8.2% vs. 15%). This variation may be explained by differences in data collection methods (medical records vs. self-report).

4.5.2 Strengths and limitations

The major strength of this study is the large national population-based sample; findings from this study provide comprehensive baseline data on the burden of diagnosed type 2 diabetes in Ireland. The longitudinal study design of TILDA will permit future analysis of trends in the prevalence of diagnosed type 2 diabetes and related complications within the older population (72).

However, several limitations need to be considered when interpreting the findings. Misclassification bias may have led to an inaccurate estimation of prevalence as case finding methods were based on self-report. When compared to medical records, data from self-report have been shown to underestimate the prevalence of diabetic retinopathy (195). However, national (173) and international (196-198) studies have indicated that compared to medical records, self-report is a suitable method to determine type 2 diabetes prevalence. Secondly, our study only included those with diagnosed type 2 diabetes and was limited to adults aged 50 years and over; therefore our prevalence estimates may underestimate the actual burden of diabetes in Ireland. Diabetes-related complications can exist in those with undiagnosed diabetes (204, 205). Irish data have demonstrated that the inclusion of undiagnosed type 2 diabetes can increase prevalence estimates up to 40% (170, 173, 203). The younger population in Ireland have lower diabetes prevalence (164); therefore prevalence rates of complications are possibly lower in this age group. Finally, certain members of the population were under-represented in the TILDA

sample; however, weights were calculated to correct for differential non-response, minimising the possibility of selection bias (19, 193).

4.5.3 Conclusions

Despite these limitations, findings from this study are useful for policy makers planning the development of diabetes services in Ireland. Further research is warranted to estimate the national prevalence of undiagnosed type 2 diabetes and determine the burden of diabetes-related complications in the younger population.

Table 7. Characteristics of the first wave TILDA sample aged 50 years and over, 2009-2011

	General population (n=7503)*	Diagnosed type 2 Diabetes (n=655)	
Variables	Total % (95% CI)	Total % (95% CI)	P
Age			
≥ 65 yrs.	40 (38-42)	57 (52- 61)	< 0.001
Location			
Dublin	26 (23-30)	28 (23-33)	0.3
Other city	30 (27-34)	32 (27-37)	
Rural	44 (40-47)	40 (35-46)	
Education			
Primary/none	37 (36-39)	51 (47-55)	< 0.001
Secondary	44 (43-45)	37 (33-41)	
Third level/higher	19(18-20)	12 (10- 15)	
Medical cover			
State assisted	35 (33-37)	50 (45- 54)	< 0.001
Private insurance	38 (36-40)	24 (20-27)	
Dual cover	16 (15-17)	19 (16- 23)	
No additional cover	11 (10-12)	7.0 (5.0-10)	
Smoking			
Never	43 (42-44)	36 (32-40)	< 0.001
Past	38 (36-38)	46 (41- 50)	
Current	20 (19-21)	19 (16-22)	
Physical activity			
Low	32 (30-33)	45 (41-50)	< 0.001
Moderate	34 (33-35)	34 (30-38)	
High	34 (32-38)	21 (18-25)	
Diagnosed			
Hypertension	36 (34-37)	63 (58-67)	< 0.001
High cholesterol	36 (35-38)	52 (48-56)	0.4
Health assessment	General population (n=5427)	Diagnosed type 2 diabetes (n=437)	<i>p</i>
BMI			
Normal	23 (22-25)	7.4 (1-10)	< 0.001
Overweight	44 (42-45)	33 (30-38)	
Obese	33 (32-34)	60 (54- 64)	
BMI (kg/m²) ‡	28 (4.5)	31 (5.1)	< 0.001
WC (cm) §	91 (63)	100 (87)	0.02
Blood pressure			
Systolic (mmHg)	135 (20)	139 (20)	< 0.001
Diastolic (mmHg)	83 (11)	81 (11)	< 0.001
Cholesterol			
HDL (mmol/l)	1.6 (0.4)	1.3 (0.3)	< 0.001
LDL (mmol/l)	2.9 (0.9)	2.2 (0.9)	< 0.001

* Excluding 17 based on Type 1 diabetes criteria

‡ Mean and standard deviation; provided for continuous variables

§ Optimal waist circumference: men ≤ 94cm; women ≤80cm

5. RISK FACTORS FOR MACRO- AND MICROVASCULAR COMPLICATIONS AMONG OLDER ADULTS WITH DIAGNOSED TYPE 2 DIABETES: FINDINGS FROM THE IRISH LONGITUDINAL STUDY ON AGEING (PAPER 3)

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(APPENDIX 10)

5.1 Abstract

Aim: To explore risk factors for macro-and micro vascular complications in a nationally representative sample of adults aged 50 years and over with type 2 diabetes in Ireland.

Methods: Data from the first wave of The Irish Longitudinal Study on Ageing (TILDA), (2009-2011) was used in cross-sectional analysis. The presence of doctor diagnosis of diabetes, risk factors and macro-and micro vascular complications were determined by self-report. Gender-specific differences in risk factor prevalence were assessed with the Chi-squared test. Binomial regression analysis was conducted to explore independent associations between established risk factors and diabetes related complications.

Results: Among 8175 respondents, 655 were classified as having type 2 diabetes. Older age, being male, a history of smoking, a lower level of physical activity and a diagnosis of high cholesterol were independent predictors of macrovascular complications. Diabetes diagnosis of 10 or more years, a history of smoking and a diagnosis of hypertension were associated with an increased risk of microvascular complications. Older age, third level education and a high level of physical activity were protective factors ($p < 0.05$).

Conclusions: Early intervention to target modifiable risk factors is urgently needed to reduce diabetes-related morbidity in the older population in Ireland.

5.2 Background

Over the past two decades, the global burden of diabetes has increased significantly (5, 207, 208). Between 1998 and 2015, the prevalence of diabetes increased from 2.2% to 5.2% among the adult population in Ireland (159). In 2010, diabetes was the ninth leading cause of mortality (208) and the 14th largest cause of disability adjusted life years (DALYs) (207) worldwide. The economic cost of diabetes is also high and will continue to rise; approximately 12% of the world's total health expenditure was spent on diabetes in 2010 (32). The vast majority of this burden is attributable to the macrovascular (myocardial infarction, congestive cardiac failure, cerebrovascular accident) and microvascular (diabetic neuropathy, retinopathy, and nephropathy) complications of diabetes (5). The Cost of Diabetes in Europe - Type II study reported that 72% of people had at least one diabetes-related complication (59). In Ireland, the prevalence of macro- and micro vascular complications among adults aged 50 years and over with type 2 diabetes is 15% and 26% respectively (178).

Compared to the general population, individuals with type 2 diabetes are at an increased risk of developing CVD (47, 48). Type 2 diabetes is also a significant cause of blindness in adults, non-traumatic lower limb amputations, and end-stage renal disease resulting in transplantation and dialysis (5). We reported that the risk of visual impairment, in adults aged 50-69 years, is approximately four times higher in the population with diabetes compared to those without diabetes (209). Buckley et al. (14) found that the risk of an individual with diabetes undergoing lower-leg amputation was 22 times that of an individual without diabetes.

Time-related variables, such as age and longer diabetes duration are associated with the onset of diabetes related complications (78). Established risk factors for CVD such

as hypertension, high cholesterol and smoking further increase the likelihood of developing both macro- and micro vascular complications (86). Socio-economic status (SES) has also been identified as a predictor of microvascular complications. Lower educational attainment is considered to influence the development of such complications through health behaviours, access to care and processes of diabetes care (98, 102, 103). While the national prevalence of diagnosed type 2 diabetes and related complications has been established among older population in Ireland (178), evidence on the individual level risk factors for macro- and micro- vascular complications is lacking. Identification and treatment of risk factors can delay or prevent the development of diabetes related complications (5). Therefore, the purpose of this paper is to identify the determinants of macro- and micro -vascular complications among adults aged 50 years and over with diagnosed type 2 diabetes.

5.3 Methods

5.3.1 Data source

Data from the first wave (2009-2011) of The Irish Longitudinal Study on Ageing (TILDA) a population-based prospective cohort study of community- dwelling adults aged 50 and over in Ireland were used in this cross-sectional analysis (19). A nationally representative sample was selected using the RANSAM sampling technique from a listing of all residential addresses in the Republic of Ireland (The Irish Geodirectory) (210). A total of 8175 adults aged 50 years and over completed a computer-assisted personal interview (CAPI), representing a household response rate of 62%. The CAPI was administered by trained social interviewers in participants' homes. This recorded detailed information on health, social, and economic circumstances. During the CAPI, participant's reported their medication use and

interviewers noted the correct name from the medication packaging. Medications were assigned the WHO Anatomic Therapeutic Chemical (ATC) classification codes (168). Ethical approval was obtained from the Faculty of Health Sciences Research Ethics Committee of Trinity College Dublin. Written informed consent was provided by all respondents before participation (19).

5.3.2 Type 2 diabetes classification

Methods to classify diagnosed type 2 diabetes and macro- and micro- vascular complications have been reported in detail elsewhere (178). In brief, individuals were classified as having diagnosed diabetes if they self-reported a previous doctor diagnosis or if they reported the use of insulin or oral hypoglycaemic agents during the CAPI. Age at diabetes diagnosis (years) was established by self-report. Anyone aged less than 40 years at diagnosis and injecting insulin but not on oral hypoglycaemic agents was classified as having type 1 diabetes; all others were classified as having diagnosed type 2 diabetes (178).

5.3.3 Macrovascular and microvascular complications

All TILDA participants were asked the question *“Has a doctor ever told you that you have any of the conditions on this card?”* Heart attack (Myocardial infarction), heart failure (congestive cardiac failure), stroke (cerebrovascular accident) and mini stroke (TIA) were included in the list and were defined as macrovascular complications. Participants who reported a doctor diagnosis of diabetes were asked the question *“Has a doctor ever told you that you have any of the following conditions related to your diabetes?”* The conditions listed were: leg ulcer, protein in urine (proteinuria), lack of feeling and tingling pain in legs and feet due to nerve damage (diabetic neuropathy), damage to the back of your eye (diabetic retinopathy) or damage to

your kidneys (diabetic nephropathy); these were defined as microvascular complications (178). Macro- and micro- vascular complications were collapsed into dichotomous variables, to indicate the presence or absence of at least one complication.

5.3.4 Covariates

Socio-demographic, behavioural and medical history variables were recorded in the CAPI including: sex, age (50-64 years, 65-74 years, 75+ years), location of household (Capital city [Dublin], other town/ city, rural), educational attainment (primary level or none, secondary level, third level or higher), medical care cover (means-tested public health insurance scheme for those on low incomes, supplementary private health insurance, dual cover [both state-assisted cover and private insurance], no additional cover for healthcare). Smoking status was classified as ever smoker (current and former smoker) and never smoker (non-smoker). Physical activity (low, moderate, high) was self-reported using the short version of the International Physical Activity Questionnaire (IPAQ) and categorised using the IPAQ scoring protocol (211). Duration of diabetes diagnosis was calculated by subtracting age at diagnosis from age (years) at interview and was subsequently categorised (0-4 years, 5-9 years, ≥ 10 years). The use of diabetes medication (oral hypoglycaemic agents, insulin or none) was reclassified as diet alone, oral agents alone, insulin alone, or oral agents and insulin. A previous doctor diagnosis of hypertension or high cholesterol was ascertained by self-report.

5.3.5 Statistical analysis

Analysis was carried out in Stata version 13 for windows (StataCorp, College Station, TX) using the survey function (*svy*). Inverse probability weights were applied to all

analyses to provide population estimates. Weights were calculated according to the distribution of marital status, educational attainment and geographic location using Irish census data from 2006-2010 and to the distribution of age and sex using Irish census data from 2011 (193).

Descriptive statistics were used to summarise characteristics of the population with diagnosed type 2 diabetes and were stratified by gender. Gender-specific differences in categorical variables were analysed using Pearson's chi-square test. The mean and standard deviation were reported if continuous data conformed to Normality and the student t-test was conducted to compare means. If data were skewed, the median with associated lower and upper quartile values was reported and the Mann-Whitney test was utilised.

Associations between risk factors and diabetes related complications were examined using a log-binomial regression. Risk ratios (RR) and 95% CI were generated as a measure of association. Risk factors served as independent variables and were chosen on the basis of previous literature (74, 78-83, 87-90, 98, 212-215) or if significant associations were observed in univariate analysis. A forward block-wise entry method was used with independent variables which were entered into the regression model in three blocks: 1) sociodemographic variables (age, sex and education attainment) and duration of diabetes diagnosis, 2) behavioural factors (ever smoked and level of physical activity), 3) medical history variables (diagnosis of hypertension, high cholesterol). Collinearity was assessed by the variance inflation factor (VIF); a VIF of >10 indicated multicollinearity. Statistical significance was defined as $p < 0.05$.

5.4 Results

Of the 8175 participants in TILDA, 634 participants reported a previous doctor diagnosis of diabetes and 38 participants did not report a diagnosis of diabetes but were classified as having diabetes by the use of oral hypoglycaemic agents or insulin. Of these, 17 people were classified as having type 1 diabetes and were excluded from the present analysis. Of the 655 people with type 2 diabetes, 57.7% were male and the mean age was 66.6 (SD= 8.8) years. Table 8 shows the characteristics of the population with type 2 diabetes, stratified by gender. Approximately half of participants were diagnosed with diabetes between the ages of 50-69 years (51.8% [47.6% to 55.9%]). The median time since diabetes diagnosis was 5.3 years (IQR 2 to 11 years). Approximately half the study sample had completed secondary or third level education (51.1% [46.9% to 55.4%]). In terms of disease management, 17.5% (14.8% to 20.6%) of participants managed type 2 diabetes with diet alone, 74.2% (70.6% to 77.5%) reported the use of oral hypoglycaemic agents and 7.5% (5.6% to 10.0%) reported using both oral hypoglycaemic agents and insulin. The prevalence of CVD risk factors was high among participants; 18.8% [15.8% to 22.3%]) of participants were current smokers, 62.5% (58.1% to 66.6%) reported a previous doctor diagnosis of hypertension and 51.7% (47.5% to 55.9) reported a previous doctor diagnosis of high cholesterol. Current smoking was higher among females compared to males (20.6% [15.5% to 26.5%] vs. 17.5% [13.9% to 26.5%]) and a higher proportion of males reported higher levels of physical activity (27.5% [23.2% to 32.3%] vs. 13.7% [9.6% to 19.2%]). Fifteen percent (15.1% [12.3% to 18.4%]) of participants reported a previous doctor diagnosis of at least one macrovascular complication and 26%

(25.5% to 29.9%) of participants reported a previous doctor diagnosis of at least one microvascular complication.

5.4.1 Factors associated with diabetes related complications

Table 9 presents the results from the binomial regression analyses, where previous diagnosis of at least one macrovascular complication served as the dependant variable. The risk of a macrovascular complication was higher among older participants and (RR 1.6 [1.1 to 2.5] 65 to 74 years; RR 2.0 [1.2 to 3.2] 75 years or over vs. 50 to 64 years). Female participants were less likely to report a previous diagnosis of a macrovascular complication relative to males (RR 0.6 [0.4-0.8]). Finally, individuals classified as ever smokers had a 60% increase in the risk of a macrovascular complication compared to never smokers (RR 1.6 [1.1 to 2.6]).

Table 10 presents the results from the binomial regression analyses, with previous diagnosis of at least one microvascular complication as the dependant variable. There was no evidence to suggest that the risk of microvascular complications was different in participants diagnosed less than four years compared to those diagnosed between five and nine years (RR 1.1 [0.8 to 1.7]). While participants with type 2 diabetes for 10 or more years were approximately twice as likely to have reported a microvascular complication compared to those who had been diagnosed less than four years (RR 1.9 [1.4 to 2.5]). Participants who had ever smoked were almost one and a half times more likely to report a doctor diagnosis of a microvascular complication relative to never smokers (RR 1.4 [1.1 to 2.0]). While the risk of a microvascular complication did not differ between those with a secondary level education compared to those with primary level or less (RR 0.9 [0.6 to 1.2]), the risk was significantly less in participants with a third level education (RR 0.6 [0.4 to 0.9])

compared to those with primary level or less. The risk of a microvascular complication did not differ between participants who reported a moderate level of physical activity compared to those with low level of activity (RR 0.8 [0.6 to 1.1]). However, participants in the highest physical activity category were 50% less likely to report a microvascular complication (RR 0.5 [0.3-0.8]) compared to participants with low level of activity. Participants diagnosed with hypertension were one and a half times more likely to have reported a previous diagnosis of at least one microvascular complication relative to participant's who had not reported a previous diagnosis (RR 1.5 [1.1-2.1]). Collinearity was not found between variables ($VIF \leq 2$).

5.5 Discussion

5.5.1 Main findings

To our knowledge, this is the first study to identify individual level risk factors associated with macrovascular and microvascular complications among people with type 2 diabetes in Ireland using nationally representative data. Older age, having ever smoked and a previous doctor diagnosis of high cholesterol were independently associated with an increased risk of macrovascular complications whereas being female and high levels of physical activity demonstrated a protective effect. Longer duration since diagnosis, having ever smoked and a previous doctor diagnosis of hypertension were associated with an increased risk of microvascular complications whereas achieving a third level or higher education level and high levels of physical activity demonstrated a protective effect.

Consistent with existing research (88, 89, 95), established risk factors for CVD (88, 89) and being male (88, 95) were found to be independent predictors of at least one macrovascular complication. The United Kingdom Prospective Diabetes Study

(UKPDS) reported that the risk of myocardial infarction and stroke were higher in older participants, smokers and those with high cholesterol (88, 89). Prospective studies have also identified hypertension (88-90, 214) as a risk factor for the development macrovascular complications among individuals with type 2 diabetes; however, our study failed to demonstrate a significant association with this risk factor. Our findings are not atypical of existing research in this area; the diversity of results has been discussed previously (84, 88, 89, 214) Evidence demonstrating an association between duration of diabetes diagnosis and macrovascular complications is also equivocal. Some studies are in accordance with our findings (84) whereas others have reported the opposite (78, 89). Similar to the present study, Fox et al. (84) failed to demonstrate duration of diabetes as an independent predictor of combined non-fatal macrovascular events (myocardial infarction, stroke, congestive heart failure and angina) (84). While baseline data from the ADVANCE trial (78) demonstrated that diabetes duration was an independent predictor of non-fatal myocardial infarction and non-fatal stroke among 11,140 individuals with type 2 diabetes aged 55 years and older. Unlike the previous study (78), we were unable to conduct complication-specific analysis due to the small number of reported events.

Consistent with previous research (78-83), longer duration since diabetes diagnosis was independently associated with microvascular complications. Diabetes duration reflects total glycaemic control and risk factor exposure over time (85). Likewise, both smoking and hypertension have been identified as prominent risk factors in the development of neuropathy, retinopathy and nephropathy (75, 79-81, 91, 214, 216). Similar to previous findings (79, 83, 98-101), higher educational attainment was associated with a lower likelihood of microvascular complications in the present

study. Education is a universal indicator of SES and is commonly used in cardiovascular epidemiology as it usually remains constant after early childhood and is less likely to be influenced by social changes or illness in adulthood (217). Lower educational attainment has been associated with poorer disease management, lower rates of physical activity, fewer ophthalmologic visits and fewer foot examinations (98). Earlier detection by systematic screening can prevent or delay the development of diabetes related complications. Reductions in leg amputation rates have been achieved in the UK following changes to the structure of foot care for those with diabetes (218, 219).

In the present study, the risk of microvascular complications was lower in participants who reported a high level of physical activity compared to the lowest physical activity group. This protective effect on microvascular morbidity has been highlighted previously (81). High levels of physical activity are beneficial for individuals with type 2 diabetes as it is linked with better glucose control (81). Similar to the present study, the Health and Retirement Study (HRS) in the USA (215) reported that individuals with diabetes related microvascular complications were less likely to engage in high levels of physical activity. Janevic et al. (215) suggest that the development of diabetes-related complications may cause clinical, practical and psychological barriers to engaging with physical activity. Therefore, additional support maybe needed to achieve recommended amounts of physical activity in those who have developed complications (215).

5.5.2 Strengths and limitations

The major strength of this study is the large national population-based sample and the high response rate (62%). Inverse probability weights were calculated to take into

account the under-representation of individuals with lower levels of education attainment and to adjust for the lower response rate in age and sex groupings (168). Study weights were applied to all analyses to correct for differential non-response. Therefore, selection bias was minimised and the TILDA sample is representative of the general Irish population (168).

However, several limitations need to be considered when interpreting the findings. Firstly, data used in the analyses were based on self-report and was not ascertained by an objective method. Self-reporting is a recognised limitation in all surveys due to potential inaccuracies, recall and reporting bias (194). When compared with medical records, data based on self-report have been shown to underestimate the prevalence of diabetic retinopathy (195) and heart failure (197). In the present study, the prevalence of complications may have been underestimated; as a consequence the measure of association may be biased toward the null. However, moderate to high levels of agreement, between self-report and medical records, have been demonstrated for diabetes (197, 198), myocardial infarction (197), stroke (197, 198) and hypertension (197). Data on smoking and physical activity were also based on self-report where socially desirable responses are a documented phenomenon (194).

Secondly, recall bias should be considered. Participants who were recently diagnosed with diabetes may remember the age of their diagnosis with greater precision. Incorrect reporting may result in differential misclassification and could lead to a subsequent decrease in the measure of association if the number of years since diabetes diagnosis has been overestimated. Nevertheless, the previously documented association between microvascular disease and longer duration since diagnosis (78-83) was detected in this study. Finally, a cross-sectional study design

does not permit assessment of causality. For instance, it is not possible to infer if a high level of physical activity reduces the risk of microvascular complications or whether the development of microvascular complications inhibits physical activity (215).

5.5.3 Conclusions

Despite these limitations, findings from this study are in accordance with other research from prospective cohort studies. We demonstrated that macrovascular complications were more common in the male population and the probability of microvascular complications were reduced in participants with higher educational attainment. Additionally, modifiable risk factors were independently associated with both macro- and micro vascular complications. While addressing lifestyle factors is a key part of preventing complications, delivering adequate services for people with diabetes is essential in earlier detection and management of complications. In 2010, a national diabetes programme was introduced in Ireland (7). To date, the programme has been instrumental in the roll out of a national retinal screening programme, the recruitment of Diabetes Nurse Specialists and development of a national foot care model (7). Macrovascular and microvascular complications are often preventable; therefore findings from this study are useful for policy makers planning the development of other diabetes services, including the diabetes cycle of care that has been recently introduced into primary care in Ireland (220). Diabetes prevalence is projected to increase; therefore effective prevention strategies are urgently needed to reduce the future burden of complications in Ireland.

Table 8. Descriptive characteristics of the first wave TILDA sample aged 50 years and over with diagnosed type 2 diabetes, 2009-2011

Variable	Type 2 diabetes (total n= 655)			
	Male n (%)	Female n (%)	<i>p</i>	Total % (95% CI)
Age				
Years (mean, sd.)	66.6 (9.7)	68.6 (10.4)		67.4 (10.1)
Location				
Dublin	92 (25.5)	77 (31.5)	0.17	27.9 (23.1,33.4)
Other city	113 (30.0)	84 (34.1)		31.7 (26.9,36.9)
Rural	182 (44.5)	105 (35.3)		40.3 (35.2,45.7)
Educational attainment				
Primary/none	163 (48.6)	116 (54.7)	0.12	51.1 (46.9, 55.4)
Secondary	137 (37.1)	103 (36.1)		36.7 (32.9, 40.7)
Third level/higher	89 (14.3)	47 (9.2)		12.2 (10.1, 14.6)
Medical cover				
State assisted	163 (43.9)	139 (57.8)	<0.01	49.7 (45.4, 53.9)
Private insurance	111 (27.6)	60 (17.9)		23.6 (20.3, 27.2)
Dual cover	86 (19.9)	51 (18.7)		19.4 (16.2, 23.0)
No additional cover	30 (8.5)	16 (5.6)		7.3 (5.3, 10.1)
Smoking				
Never	114 (29.9)	120 (44.0)	<0.001	35.8 (31.8, 39.9)
Past	210 (52.7)	94 (35.4)		45.5 (41.2, 49.9)
Current	66 (17.5)	52 (20.1)		18.8 (15.8, 22.3)
Physical activity				
Low	140 (36.8)	143 (56.5)	<0.001	45.0 (40.8,49.2)
Moderate	137 (35.7)	77 (29.8)		33.3 (29.5,37.2)
High	109 (27.5)	43 (13.7)		21.8 (18.5,25.5)
Age of diagnosis				
< 50 years	54 (16.4)	47 (16.8)	0.04	16.6 (13.7,19.8)
50-69 years	196 (55.9)	125 (46.2)		51.8 (47.6,55.9)
70+ years	112 (27.7)	84 (36.9)		31.6 (27.8,35.7)
Duration of DM diagnosis				
Years (median, IQR)	5.0 (1.5,12)	5.5 (2.5,15)	0.5	5.3 (2,11)
DM treatment				
Diet	64 (16.7)	53 (18.3)	0.9	17.5 (14.8,20.6)
Oral meds	293 (74.7)	190 (73.9)		74.2 (70.6,77.5)
Insulin	2 (1.0)	4 (0.8)		0.8 (0.3,1.8)
Both	31 (8.2)	19 (6.5)		7.5 (5.6,10.0)
Other medication				
Hypertension	221 (58.4)	161 (60.0)	0.6	59.1 (55.4,63.9)
High Cholesterol	164 (43.4)	130 (46.5)	0.4	44.7 (40.4,48.7)
Flu shot	286 (74.3)	212 (78.5)	0.2	76.1 (72.4,79.5)
Doctor diagnosed				
Hypertension	236 (61.2)	170 (63.8)	0.9	62.5 (58.1, 66.6)
High cholesterol	192 (50.0)	149 (54.2)	0.9	51.7 (47.5, 55.9)
DM complications				
Macro	73 (17.8)	28 (11.4)	0.04	15.1 (12.3, 18.4)
Micro	89 (25.2)	67 (26.8)	0.7	26.0 (22.5, 29.9)

Table 9. Multivariate binomial regression models exploring independent associations between predictor variables and macrovascular complications*

Predictor	Model 1 [†] RR (95% CI)	<i>p</i>	Model 2 [‡] RR (95% CI)	<i>p</i>	Model 3 [§] RR (95% CI)	<i>p</i>
Age						
50-64 years	1		1		1	
65-74 years	1.6 (1.0, 2.5)	0.05	1.5 (0.9, 2.4)	0.07	1.6 (1.1, 2.5)	0.04
75+ years	2.0 (1.3, 3.3)	0.003	1.8 (1.1, 4.1)	0.01	2.0 (1.2, 3.2)	0.005
Gender						
Male	1		1		1	
Female	0.6 (0.4, 0.9)	0.007	0.6 (0.4, 0.9)	0.009	0.6 (0.4, 0.8)	0.005
Education						
Primary/less	1		1		1	
Secondary	0.9 (0.6, 1.3)	0.5	0.9 (0.6, 1.4)	0.5	0.9 (0.6, 1.3)	0.6
Third/higher	1.1 (0.7, 1.7)	0.7	1.2 (0.7, 1.8)	0.5	1.1 (0.7, 1.7)	0.7
Duration of diagnosis						
0-4 years	1		1		1	
5-9 years	1.0 (0.6, 1.7)	0.9	0.9 (0.6, 1.6)	0.9	1.0 (0.6, 1.7)	0.9
10 + years	1.2 (0.8, 1.8)	0.4	1.1 (0.7, 1.6)	0.7	1.1 (0.8, 1.7)	0.5
Ever smoked						
No			1		1	
Yes			1.7 (1.1, 2.7)	0.02	1.6 (1.1, 2.6)	0.04
Physical activity						
Low			1		1	
Medium			0.8 (0.6, 1.2)	0.3	0.9 (0.6, 1.2)	0.5
High			0.5 (0.3, 0.9)	0.01	0.5 (0.3, 0.9)	0.03
Previous hypertension						
No					1	
Yes					1.1 (0.8, 1.7)	0.5
Previous high cholesterol						
No					1	
Yes					1.7 (1.1, 2.5)	0.008

* Indicating report of at least one macrovascular complication (heart attack, congestive heart failure, stroke or TIA)

[†] Variables entered in Model 1: age, sex, education, years since diagnosis

[‡] Variables entered in Model 2: age, sex, education, years since diagnosis, smoking status, physical activity

[§] Variables entered in Model 3: age, sex, education, years since diagnosis, smoking status, physical activity, doctor diagnosed hypertension, doctor diagnosed high cholesterol

Table 10. Multivariate binomial regression models exploring independent associations between predictor variables and microvascular complications*

Predictor	Model 1 [†] RR (95% CI)	<i>p</i>	Model 2 [‡] RR (95% CI)	<i>p</i>	Model 3 [§] RR (95% CI)	<i>p</i>
Age						
50-64 years	1		1		1	
65-74 years	0.8 (0.6, 1.2)	0.4	0.9 (0.7, 1.2)	0.4	0.9 (0.7, 1.1)	0.3
75+ years	0.7 (0.5, 1.1)	0.1	0.7 (0.5, 0.9)	0.02	0.6 (0.5, 0.9)	0.01
Gender						
Male	1		1		1	
Female	1.0 (0.8, 1.4)	0.9	1.1 (0.7, 1.3)	0.8	1.0 (0.8, 1.3)	0.9
Education						
Primary/less	1		1		1	
Secondary	0.9 (0.7, 1.2)	0.4	0.9 (0.7, 1.2)	0.5	0.9 (0.7, 1.2)	0.5
Third/higher	0.6 (0.4, 0.8)	0.007	0.5 (0.4, 0.9)	0.02	0.6 (0.4, 0.9)	0.02
Duration of diagnosis						
0-4 years	1		1		1	
5-9 years	1.2 (0.8, 1.8)	0.3	1.1 (0.8, 1.6)	0.5	1.1 (0.8, 1.7)	0.5
10+ years	2.0 (1.5, 2.7)	0.000	1.8 (1.4, 2.5)	0.000	1.9 (1.4, 2.5)	0.000
Ever smoked						
No			1		1	
Yes			1.4 (1.1, 2.0)	0.03	1.4 (1.1, 2.0)	0.02
Physical activity						
Low			1		1	
Medium			0.7 (0.6, 1.0)	0.1	0.8 (0.6, 1.1)	0.1
High			0.5 (0.3, 0.7)	0.001	0.5 (0.3, 0.8)	0.003
Hypertension						
No					1	
Yes					1.5 (1.1, 2.1)	0.006
High cholesterol						
No					1	
Yes					1.0 (0.8, 1.3)	0.9

* Indicating report of at least one microvascular complication (leg ulcer, protein in urine, neuropathy, retinopathy or damage to kidneys)

[†] Variables entered in Model 1: age, sex, education, years since diagnosis

[‡] Variables entered in Model 2: age, sex, education, years since diagnosis, smoking status, physical activity

[§] Variables entered in Model 3: age, sex, education, years since diagnosis, smoking status, physical activity, doctor diagnosed hypertension, doctor diagnosed high cholesterol

6. TRENDS IN BLINDNESS DUE TO DIABETIC RETINOPATHY AMONG ADULTS AGED 18-69 YEARS OVER A DECADE IN IRELAND (PAPER 4)

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(APPENDIX 10)

6.1 Abstract

Aim: To describe trends in the incidence of visual impairment and blindness due to diabetic retinopathy among adults aged 18-69 years in Ireland between 2004 and 2013.

Methods: Data on visual impairment due to diabetic retinopathy in adults aged 18-69 years or over who are registered with the National Council for the Blind of Ireland, (2004-2013) were analysed. Annual incidence rates were calculated for the adult population and the population with diagnosed diabetes. Poisson regression was used to test for changes in rates over time. The relative, attributable and population risk of blindness and visual impairment due to diabetic retinopathy were calculated for 2013.

Results: Over the decade, the prevalence of diagnosed diabetes increased from 2.1% to 3.6%. Among people with diagnosed diabetes, the incidence of visual impairment due to diabetic retinopathy increased from 6.4 (95% CI 2.4-13.9) per 100,000 in 2004 to 11.7 (95% CI 5.9-21.0) per 100,000 in 2013. The incidence of blindness due to diabetic retinopathy varied from 31.9 per 100,000 (95% CI 21.6-45.7) in 2004 to 14.9 per 100,000 (95% CI 8.2-25.1) in 2013.

Conclusions: Our findings indicate the need for increased attention to preventive measures for microvascular complications among adults with diabetes in Ireland. Retinopathy screening has been standardised in Ireland, these findings provide useful baseline statistics to monitor the impact of this population-based screening programme.

6.2 Background

Vision impairment is a major public health problem worldwide (222). In 2010, it was estimated that 0.5% of the global population were blind (222). In Ireland, the prevalence of blindness increased from 0.2% in 2003 (175) to 0.3% in 2010 (223). Worldwide approximately 80% of visual impairment cases can be prevented or cured (224). In order to reduce the global burden of visual impairment, nine preventable causes of visual impairment have been prioritised on the global public health agenda including diabetic retinopathy (224). Compared to the general population, individuals with diabetes are at an increased risk of losing their eyesight (5). Genz et al. found that the risk of blindness in an individual with diabetes was 2.4 times that of an individual without diabetes (53). In Ireland there is no diabetes register or national data-capture system to observe diabetes trends in diabetes incidence or prevalence over time. However, findings from a recent systematic review (159) suggest that the prevalence of diagnosed diabetes increased from 2.2% in 1998 to 5.2% in 2015. The review was unable to distinguish between the various types of diabetes (159); however it can be assumed that type 2 diabetes is driving the increase in prevalence as it accounts for 90 % of all diabetes cases (2). As the prevalence of diabetes rises, visual impairment due to diabetic retinopathy represents a growing global public health challenge (73).

Diabetic retinopathy is a leading cause of preventable vision loss in countries such as the UK (225) and the USA (226). In Ireland, it was the second most common cause of blindness among adults aged 16-64 years in 2003, with an incidence rate of 0.7 per 100 000 adults (175). Retinitis pigmentosa was the most common cause of blindness among adults aged 16-64 years in 2003; with an incidence rate of 0.9 per 100 000

adults (175). The individual and societal costs of visual impairment due to diabetic retinopathy are significant (50, 227), and include increased healthcare costs (228, 229), loss of productivity (229), and severe reduction in healthy life years (230) and quality of life (231).

It is now widely accepted that systematic screening for diabetic retinopathy has the potential to reduce the incidence of sight-threatening visual impairment (232). A reduction of rates of blindness due to diabetic retinopathy have been noted in countries that have established population-based retinal screening programmes as part of their national diabetes strategy (53, 66, 67, 233-235). Up until recently, there was no national population-based screening programme for diabetic retinopathy in Ireland; screening was delivered on a limited basis by local services using different models of service provision (236). In 2013, a national retinal screening programme (Diabetic Retinascreen) was introduced in Ireland (122) with the objective of reducing blindness by 40% through the implementation of a standardised screening and treatment service (7). The service was introduced on a phased basis, patient registration began in 2013 and full implementation was achieved in late 2014.

In 2010, the WHO highlighted the importance of within-country data on visual impairment to facilitate global efforts aimed at monitoring and eliminating avoidable blindness (224). Given that the national programme has only been recently introduced, there is limited national data on rates of visual impairment due to diabetic retinopathy in Ireland (159). Therefore, this study used national blind registry data to establish current rates of visual impairment and blindness due to diabetic retinopathy. Data from blind registers allow the absolute burden of visual impairment attributed to diabetic retinopathy to be quantified (237). In Ireland, blind

registry data have been previously used to describe trends in all-causes of blindness in 1996 (238) and 2003 (175). The aims of this study were to 1) estimate the incidence of visual impairment and blindness due to diabetic retinopathy among (a) the total adult population and (b) population with diagnosed diabetes in Ireland over a ten year period (2004-2013); 2) explore whether these rates have changed over time and 3) estimate the relative, attributable and population attributable risk of visual impairment and blindness due to diabetic retinopathy in Ireland in 2013.

6.3 Methods

6.3.1 Data source

Data from the National Council for the Blind of Ireland (NCBI) were analysed. The NCBI is a charitable organisation which provides support and services to people experiencing sight loss (20). Anyone who is having significant difficulty with their eyesight can be referred to the NCBI by a health care professional or family member; self-referral is also possible (20). Once referred, the individual's information is added to the NCBI database; however, an ophthalmic assessment report (OAR), to confirm the level of visual impairment, is necessary to officially register with the service (20). Registration with the NCBI is not compulsory, however those who register can access a range of NCBI support services and registration is also required to qualify for the state-provided Blind Welfare Allowance (239). The NCBI registry comprises data on approximately 15 causes of visual impairment and blindness, including macular degeneration, glaucoma, cataract, optic atrophy, retinitis pigmentosa and diabetic retinopathy (175, 223). Information such as service-user demographics (gender and date of birth), date of registration, visual acuity score and cause of visual impairment are recorded on a centralised national database. Information on type of diabetes, the

stage of diabetic retinopathy, or risk factors for diabetic retinopathy are not recorded. In this study, anonymised data on visual impairment due to diabetic retinopathy in adults aged 18-69 years, (January 2004-December 2013) were obtained for analysis.

6.3.2 Numerator data

The number of new cases of visual impairment due to diabetic retinopathy was extracted from the NCBI database for each calendar year. The number of new cases due to all other causes of visual impairment was extracted for 2013. Cases were excluded if visual acuity score was not recorded. In Ireland, visual impairment is categorised into three levels: mild visual impairment (visual acuity between 6/12 and 6/18 inclusive), moderate visual impairment (best-corrected acuity of less than 6/18 but better than or equal to 6/60 in the better-seeing eye) and blindness (visual acuity of 6/60 or less in the better eye or a visual field restricted to 20 degrees or less) (240). These criteria are commonly used in North America, Australia, and most of Europe (240). For the purpose of this study, individuals who met the national criteria for mild and moderate visual impairment were defined as 'visual impairment' and those who met the criteria for blindness were defined as 'blind'.

6.3.3 Denominator data

Annual population estimates were obtained from the Central Statistics Office (CSO), Ireland (241). A census took place in Ireland in 2006 and 2011; data for other study years were CSO inter-censal estimates (241). A diabetes register does not exist in Ireland, therefore rates for diagnosed diabetes was taken from model estimates; methods have been described in detail previously (159). In brief, using data from four nationally representative population-based studies, multivariate Poisson regression

models were undertaken to impute annual gender and age-specific (18–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years) rates of diagnosed diabetes. These gender and age-specific rates were applied to 2004–2013 population data so the absolute number of diabetes cases could be obtained. For the purpose of this study, the absolute number of diabetes cases was categorised into two age groups (18–49 years, 50–69 years). The population without diagnosed diabetes was calculated by subtracting the estimated population with diabetes in 2013 from the total population in 2013.

6.3.4 Incidence calculations

The incidence of visual impairment and blindness due to diabetic retinopathy in the total population and the population with diagnosed diabetes was calculated for each year 2004–2013; using data from the NCBI as the numerator and the census and estimated diabetes population as the denominator for the total population and diagnosed diabetes populations respectively. The incidence of visual impairment and blindness due to all other causes in the population without diagnosed diabetes was calculated for 2013; using data from the NCBI as the numerator and the estimated population without diabetes as the denominator. Rates were expressed per 100,000 population.

6.3.5 Statistical analysis

Age-standardised rates in the total population and the population at risk (in 10-year age groups) were calculated using the direct standardisation method, based on the age distribution of the last census in Ireland (2011) and the estimated population with diagnosed diabetes in 2011, respectively; 95% confidence intervals (95% CI) were based on the Poisson distribution. Mean incidence figures, with standard

deviations (SD) and 95% CI's, were calculated for the decade. The risk of visual impairment increases with age (63); therefore analysis was stratified by two arbitrary age groups (18-49 years, 50-69 years). Poisson regression models, using extra Poisson variation, were undertaken to explore variations in rates over time and to examine departures from linearity between 2004 and 2013. Sensitivity analysis, comparing rates in the total population between census year (2006 and 2011) was also carried out. The number of cases served as the dependant variable, year of registration served as the continuous independent variable and population was entered as the exposure variable. If this model indicated significant changes in the incident rate ratio (IRR) over time (p_{change}), the likelihood ratio test was undertaken to assess linearity. A model including year of registration as a categorical variable was compared to the model with year as registration as a continuous variable. Linearity was determined by an insignificant likelihood ratio test (p_{trend}). The IRR with corresponding 95% CI were reported if linearity was established. A two-sided $p < 0.05$ was considered statistically significant.

Age-specific relative risks of blindness and visual impairment (diabetes vs. no diabetes) in 2013 were calculated by dividing the rates in the estimated population with diabetes by the rates in the population without diabetes. The attributable risk (AR) [$\text{incidence}_{\text{exposed}} - \text{incidence}_{\text{unexposed}}$], attributable risk percent (AR %) [$\text{AR} / \text{incidence}_{\text{exposed}} * 100$], population attributable risk (PAR) [$\text{incidence}_{\text{population}} - \text{incidence}_{\text{unexposed}}$] and the population attributable risk percent (PAR %) [$\text{PAR} / \text{incidence}_{\text{population}} * 100$] were also calculated. The AR measures the excess risk attributed to diabetes, using the difference between the risk in individuals with diagnosed diabetes (exposed) and that in individuals without diabetes (unexposed).

The PAR measures the excess risk between the risk in the total population in the total population and that in individuals without diagnosed diabetes (unexposed). Analysis was carried out in Stata 13.

6.4 Results

A total of 357 new cases of diabetic retinopathy were registered with the NCBI during the 10 year period; 16 cases (5%) were excluded as an OAR had not been returned to the NCBI, therefore the level of visual impairment could not be determined. The distribution of these cases over the study period is shown in Supplementary file 1 (Appendix 4). Therefore, 341 new cases were available for inclusion in the current analysis. Between 2004 and 2013, a total of 86 cases were newly registered as visually impaired (Appendix 4; supplementary file 2); of these 67% were male and the median age was 62 years (IQR 57-66). The highest proportion of new cases of visual impairment also occurred in those aged 50-59 years (50-69 years: 73 vs. 18-49 years: 13). A total of 255 patients were newly registered as blind (Appendix 4; Supplementary file 3); of these, 58% were male and the median age of registration was 59 years (IQR 51-65). The highest number of new blind cases occurred in those aged 50-69 years (50-69 years: 195 vs. 18-49 years: 60). During 2013, 207 people (87 visually impaired and 120 blind), were newly registered on the NCBI database due to all other causes.

Over the ten year period, the prevalence of diagnosed diabetes increased from 2.1 % (95% CI: 2.0-2.2) in 2004 to 3.6% (95% CI: 3.5-3.7) in 2013; ($p_{\text{trend}} = <0.001$). Table 11 shows the number of new cases for each year, the total adult population, the estimated adult population with diabetes, the standardised incidence of visual impairment and blindness attributed to diabetic retinopathy. Between 2004 and

2013, the mean annual incidence of visual impairment due to diabetic retinopathy was 0.3 per 100,000 population (SD: 0.09; 95% CI: 0.2-0.4) and 10.7 per 100,000 population with diagnosed diabetes (SD: 2.9; 95% CI: 8.6-12.7). During the same time period, the mean annual incidence of blindness due to diabetic retinopathy was 0.9 per 100,000 adults (SD: 0.24; 95% CI: 0.7-1.04) and was 33.2 per 100,000 population with diagnosed diabetes (SD: 10.2; 95% CI: 25.9-40.5).

6.4.1 Trends in the incidence of visual impairment and blindness due to diabetic retinopathy

Over a decade, the incidence of visual impairment due to diabetic retinopathy increased in both the total population (IRR: 1.08 [95% CI: 1.01-1.16]; $p_{\text{trend}}=0.93$) and the population with diagnosed diabetes (IRR: 1.05 [95% CI: 1.02-1.1]; $p_{\text{trend}}=0.79$). In contrast, the incidence of blindness due to diabetic retinopathy in the total population did not significantly change during the study period ($p_{\text{change}}=0.73$). Over the 10 year period, the annual incidence in the population with diabetes did vary between years ($p_{\text{change}}=0.01$); however, there was no evidence of a linear trend ($p_{\text{trend}} < 0.01$).

6.4.2 Age-specific trends in the incidence of visual impairment and blindness due to diabetic retinopathy

Figure 6b illustrates the age-specific trends of visual impairment between 2004 and 2013. Among adults aged 18-49 years, the incidence remained steady in the total population (2004: 0.05 [95% CI 0.001-0.3] to 2013: 0.04 [95% CI 0.001-0.4] per 100,000; $p_{\text{change}}=0.56$), whereas among people with diabetes, the incidence ranged from 5.4 (95% CI 0.1-30.0) in 2004 to 2.3 (95% CI 0.05-12.8) per 100,000 in 2013 but did not significantly change overtime ($p_{\text{change}}=0.83$). In contrast, among adults aged 50-69 years, the incidence increased in both the total population (2004: 0.3 [95% CI

0.08-1.2] to 2013: 1.3 [95% CI 0.6-2.2]; [IRR: 1.09 [1.05-1.13]; $p_{\text{trend}}=0.92$) and the population with diabetes (2004: 7.6 [95% CI 15.8-22.5] to 2013: 18.1 [95% CI 9.4-31.6]); [IRR: 1.05 [95% CI: 1.02-1.09]; $p_{\text{trend}}=0.92$).

Figure 6c illustrates age-specific trends of blindness due to diabetic retinopathy between 2004 and 2013. Among adults aged 18-49 years, the incidence remained stable in the total population (2004: 0.2 [95% CI 0.08-0.5] to 2013: 0.2 [95% CI 0.07-0.6] per 100,000; $p_{\text{change}}=0.56$). However, among people with diabetes, the incidence ranged from 26.9 (95% CI 8.7-62.8) per 100,000 in 2004 to 11.5 (95% CI 3.7-26.8) per 100,000 in 2013 but did not significantly change overtime ($p_{\text{change}}=0.45$). Among adults aged 50-69 years, the incidence also remained stable in the total population (2004: 1.7 [95% CI 0.9-2.9] to 2013: 1.2 [95% CI 0.5-2.1] per 100,000; $p_{\text{change}}=0.15$). While among people with diabetes, the incidence varied from 33.3 (95% CI 17.7-56.9) in 2004 to 16.6 (95% CI 8.3-29.7) per 100, 000 in 2013 ($p_{\text{change}}=0.03$); however, there was no evidence of a linear trend ($p_{\text{trend}} < 0.01$).

6.4.3 Sensitivity analysis: trends in the total population between census years (2006-2011)

The results from the sensitivity analysis demonstrated that the incidence of visual impairment ($p_{\text{change}}=0.31$) or blindness ($p_{\text{change}}=0.59$) due to diabetic retinopathy in the total population did not significantly change between 2006 and 2011. Among adults aged 18-49 years, the incidence of visual impairment and blindness remained stable (visual impairment: 2006: 0.05 [95% CI 0.08-0.5] to 2011: 0.09 [95% CI 0.07-0.6] per 100,000; $p_{\text{change}}=0.98$; blindness: 2006: 0.3 [95% CI 0.08-0.5] to 2011: 0.3 [95% CI 0.07-0.6] per 100,000; $p_{\text{change}}=0.37$). Among adults aged 50-69 years, the incidence of visual impairment ranged from 0.6 (95% CI 17.7-56.9) in 2006 to 1.0

(95% CI 8.3-29.7) per 100, 000 in 2011 but did not significantly change over time ($p_{\text{change}}=0.37$). While, the incidence of blindness remained stable (2006: 2.6 [95% CI 0.08-0.5] to 2011: 2.4 [95% CI 0.07-0.6] per 100,000; $p_{\text{change}}=0.51$).

6.4.4 Relative risk, attributable and population attributable risk of visual impairment and blindness in 2013

The relative risk, attributable and population attributable risk of visual impairment and blindness in 2013 are shown in Table 12. In adults aged 18-49 years, the risk of blindness was 5.6 times higher in the population with diabetes compared to those without diabetes. In 2013, 9% of the risk of blindness in the entire population was attributable to diabetes. In adults aged 50-69 years, the risk of visual impairment was 3.9 times higher in the population with diabetes compared to those without diabetes. Sixteen per cent of the risk of visual impairment in the entire population was attributable to diabetes in 2013.

6.5 Discussion

6.5.1 Main findings

To our knowledge, this is the first study to describe national rates of registered blindness and visual impairment due to diabetic retinopathy among the population with diagnosed diabetes in Ireland. We observed a change in the incidence of blindness due to diabetic retinopathy among people with diabetes over the study period, however there was insufficient evidence to confirm a downward trend. This is in accordance with previous research describing national trends in the incidence of lower leg amputations between 2005 and 2009 among the population with diabetes (14). Findings from the present study are in contrast to international research where a decrease in the incidence of blindness (53, 67, 69, 225, 234, 235, 242, 243) and other diabetes related complications (72) has been documented. It has been

suggested that while the rates of some diabetes complications has decreased, the absolute number of cases will continue to rise because of the rising prevalence of diabetes (72). In the present study, we observed an increase in the prevalence of diagnosed diabetes; longer duration of diabetes diagnosis is an established risk factor for diabetic retinopathy (73). After 20 years of diabetes, nearly all individuals with type 1 diabetes and more than two-thirds of individuals with type 2 diabetes will develop some degree of retinopathy (50). Therefore it is possible that the full impact of the diabetes epidemic has not yet been realised in Ireland. In contrast, an increase in visual impairment was evident in the total population and among people with diabetes.

Comparison with other countries is limited due to differences in visual impairment criteria, differing age ranges and varying methods used to estimate the population at risk. In the UK, from 2000 to 2009, Hall et al. (234) described a decrease in the incidence of blindness attributable diabetes from 1.43 to 1.10 per 100,000 total population, and 59.7 to 23.9 per 100,000 population with diagnosed diabetes. However, unlike the present study, these rates included adults over 70 years rather than being restricted to adults aged 18-69 years. Elsewhere in the UK, between 2001 and 2005, the mean annual incidence of blindness due to diabetic retinopathy among adults aged 16-64 years with diabetes was 22 per 100,000 population (233). This estimate is lower than our mean annual estimate (33 per 100,000); however the sample in our study was older on average (59 years vs. 55 years) which could lead to a higher rate of blindness (63). In the USA, The Wisconsin Epidemiologic Study of Diabetic Retinopathy, reported a decline in the incidence of severe visual impairment over a 25 year period among those with type 1 diabetes (244).

Decreasing trends of blindness and visual impairment due to diabetic retinopathy have been attributed to a combination of factors, including improvements in disease management and risk factor control, earlier detection and treatment of diabetic retinopathy through the implementation of standardised retinopathy screening programmes (66, 70). In Ireland, data on risk factors for diabetic retinopathy are not routinely collated at a population-level, therefore we were unable to quantify trends in mean HbA1c levels or mean blood pressure during the study period. Prior to the introduction of the national diabetic retinal screening programme, there was wide variation in the delivery of diabetic retinopathy screening in Ireland (236). Regional screening initiatives may have contributed to the changing incidence of visual impairment and blindness observed in the present study. We found that the incidence of visual impairment due to diabetic retinopathy almost doubled over a ten year period; this may be indicative of local efforts to screen for diabetic retinopathy. The initial introduction of a screening programme results in the detection of more diabetic retinopathy cases (66). Countries that have introduced population-based retinal screening programmes have observed a decline in the frequency (66) and treatment (70) of sight-threatening diabetic retinopathy over time. The national programme was fully implemented in 2014; we hypothesize that initially, the increasing trend in visual impairment due to diabetic retinopathy will continue and will gradually decline post-implementation.

6.5.2 Strengths and limitations

The strengths of our study include the analysis of a national centralised database that has been previously used in Ireland to describe rates of all-causes of blindness in 1996 (238) and 2003 (175). To our knowledge, rates of blindness due to diabetic

retinopathy have not been estimated since 2003. Furthermore, the risk of visual impairment attributable to diabetes has not been previously reported within the Irish population.

However, our study has some limitations that must be considered. Firstly, implications of using blind registry data to describe rates in visual impairment and blindness have been discussed elsewhere (175, 234, 245). It has been suggested that blind registry data may be incomplete, leading to an underestimation the true burden of blindness. For example, data from the UK (246) have demonstrated that partially sighted individuals are less likely to be registered than blind patients. In Ireland, both visually impaired and blind individuals can avail of the services provided by the NCBI (20). However, selection bias due to an underreporting of visual impairment cases maybe possible as, unlike blindness, registration to the NCBI is not financially incentivised (239). Referral to the NCBI also may depend on severity of visual impairment further increasing the possibility of self-selection. Therefore, in the present study the annual incidence of visual impairment may be underestimated.

Previous studies have shown that 21-50% (175, 245, 246) of patients are not listed on blind registers; furthermore, partially sighted individuals are less likely to be registered than blind patients (246). Non-registration has been associated with temporary and treatable causes of blindness (175, 246); however, blindness due to diabetic retinopathy is irreversible and there is no evidence to suggest that under-registration is more likely in those with diabetes. It is also recognised that blind registry data is only a surrogate measure of incident blindness (234, 246), where changes in rates may reflect reporting differences over time rather than true changes in disease incidence. In the present study, it is possible that the NBCI may have

become a better known resource over time thereby impacting registration to the service. For instance, our findings demonstrated a sharp increase in the number of blind cases during 2008, which resulted in a sharp increase in incidence. This increase may be attributable to a national campaign specifically highlighting diabetic retinopathy among the general population, which in turn may have increased recording rates to the NCBI during this year. Nevertheless, in the absence of any other national data source, blind registries are useful for monitoring trends in diabetes-related blindness (237).

Secondly, similar to previous research (14, 233, 247), we applied secondary data to model our annual diabetes prevalence estimates. We acknowledge that the accuracy of our calculations is dependent on the reliable estimation of the population with diagnosed diabetes. For instance, an underestimation of diabetes cases in our denominator would result in an increase in our attributable risk calculations. In the absence of a national diabetes register, annual estimates on the prevalence of diabetes are lacking (159). However, our model estimates are derived from four nationally representative studies and the increasing prevalence of diagnosed diabetes among the adult population in Ireland is in accordance with other countries (159). Therefore the diabetes prevalence estimates used in the present study are the best available in Ireland. Additionally, in accordance with previous research (53, 234, 235, 247), our denominator data does not include those with undiagnosed diabetes; we acknowledge that this would result in an overestimation of rates. Finally, we could not stratify our analysis by diabetes type and duration of disease was unknown. Our rates in the youngest age group serve as a proxy for those with type 1 diabetes

mellitus, although the small number of cases in the youngest age group could introduce imprecision into our estimates.

6.5.3 Conclusions

Despite these limitations our research provides contemporary data on the trends of diabetes related complications among adults aged between 18 and 69 years in Ireland (159). Diabetic retinopathy is potentially preventable by adequate risk factor control (50). Additionally, early detection and timely treatment can prevent the onset of sight threatening visual impairment (50, 232) . Our risk calculations indicate that in 2013, prevention or early detection of diabetic retinopathy may have resulted in 82% fewer new cases of blindness in adults aged 18-49 years and 48% fewer new cases of blindness in adults aged 50-69 years. Although causality cannot be inferred in the present study, our findings highlight the need to focus on preventive measures for microvascular complications among people with diabetes in Ireland.

Evidence suggests that younger adults (149, 154, 248) and those with type 1 diabetes (149, 154, 248) are less likely to attend regular retinal screening examinations; non-attendance is a risk factor for poor visual outcomes (66). Therefore, further research is required to explore patterns of retinal screening attendance among these groups in Ireland. It is essential to develop an understanding of the factors which influence the uptake of the national diabetic retinal screening programme in order for this new investment to be effective (116). Findings from this research will provide useful baseline statistics to monitor the future impact of the national diabetic retinal screening programme (122).

Table 11. New registrations resulting from diabetic retinopathy, estimated population data and the standardised incidence of visual impairment and blindness, Ireland 2004-2013.

Year	Adult population		Number of new cases due to diabetic retinopathy		Incidence of visual impairment due to diabetic retinopathy (per 100,000 pop [95 % CI])		Incidence of blindness due to diabetic retinopathy (per 100,000 pop [95 % CI])	
	Total	Diagnosed diabetes	Visual impairment	Blindness	Total	Diagnosed diabetes	Total	Diagnosed diabetes
2004	2712428	57628	4	18	0.16 (0.05-0.3)	6.4 (2.4-13.9)	0.68 (0.4-1.0)	31.9 (21.6-45.7)
2005	2789808	61881	6	19	0.23 (0.09-0.4)	9.6 (4.4-18.2)	0.72 (0.5-1.0)	29.9 (19.8-43.2)
2006	2879284	65829	6	28	0.23 (0.09-0.4)	8.9 (3.9-17.6)	1.01 (0.6-1.4)	42.7 (30.5-58.1)
2007	2990318	71893	8	25	0.26 (0.1-0.5)	11.7 (5.7-20.9)	0.87 (0.5-1.3)	35.2 (24.2-49.4)
2008	3061169	77777	9	42	0.29 (0.1-0.5)	10.6 (5.1-19.6)	1.43 (1.0-1.9)	54.4 (40.5-71.5)
2009	3077885	83627	5	26	0.16 (0.5-0.4)	6.4 (2.3-13.9)	0.87 (0.5-1.3)	33.1 (22.5-46.9)
2010	3075576	89651	13	27	0.42 (0.2-0.7)	15.9 (8.9-26.4)	0.87 (0.6-1.3)	31.9 (21.6-45.7)
2011	3077810	96470	11	29	0.35 (0.2-0.6)	12.3 (6.1-22.0)	0.94 (0.6-1.4)	30.9 (20.7-44.4)
2012	3052159	102775	12	25	0.39 (0.2-0.7)	13.4 (6.9-23.4)	0.81(0.5-1.2)	26.7 (17.3-39.4)
2013	3032956	109842	13	16	0.39 (0.2-0.7)	11.7 (5.7-21.0)	0.52 (0.3-0.8)	14.9 (8.2-25.1)

Table 12. Relative, attributable and population attributable risk of visual impairment and blindness in Ireland, 2013.

	VI	Blindness
Relative risk (95% CI)		
No diabetes	1	1
18-49 years	1.7 (0.2-12.3)	5.5 (2.2-13.6)
50-69 years	3.9 (2.0-7.4)	1.9 (1.1-3.6)
AR /100,000 diabetes pop		
18-49 years	1.0 (-0.03-7.4)	9.4 (0.7-19.4)
50-69 years	13.4 (3.1-23.7)	7.8 (2.2-17.8)
AR % in diabetes pop		
18-49 years	44.6 (-3.9-94.5)	81.6 (53.7-92.7)
50-69 years	74.2 (51.0-86.4)	47.7 (8.4-71.9)
PAR /100,000 pop		
18-49 years	0.02 (-2.2-7.3)	0.3 (0.01-10.3)
50-69 years	0.9 (0.04-15.2)	0.5 (1.5-13.7)
PAR % in total pop		
18-49 years	1.7 (-4.7-18.7)	8.5 (0.3-17.9)
50-69 years	16.8 (4.5-28.7)	5.9 (1.8-13.1)

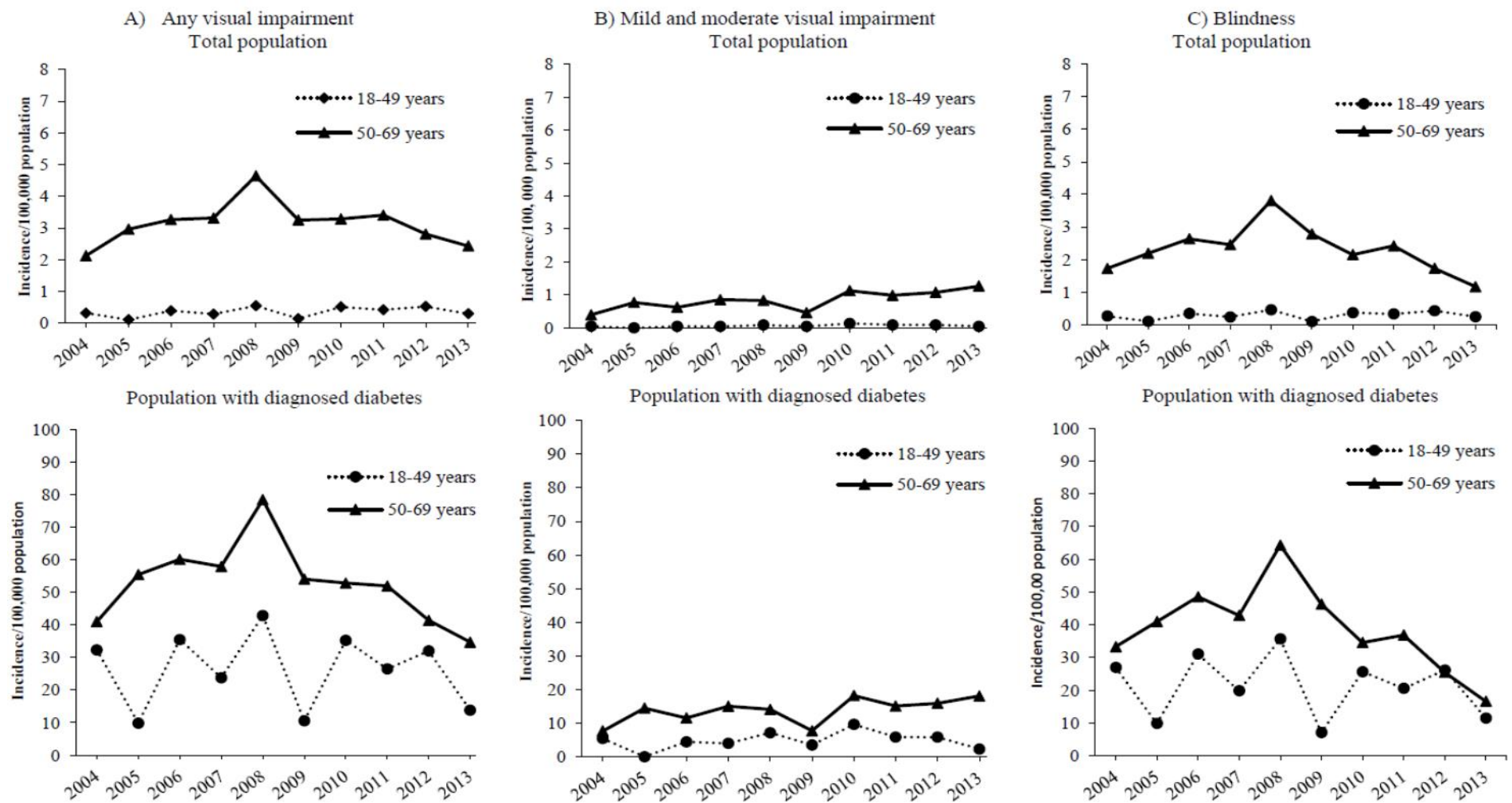


Figure 6. Age specific trends in the incidence of A) Any visual impairment; B) Mild and moderate visual impairment and C) Blindness due to diabetic retinopathy among the total adult population and adults with diagnosed diabetes, Ireland 2004-2013.



Tracey, M. L. 2017. Public health burden of diabetes in Ireland: time trends, determinants of complications and the implementation of a public health intervention to improve health outcomes for people with diabetes. PhD Thesis, University College Cork.

Please note that Chapters 7,8,9 &10 (pp.122-266) are unavailable due to a restriction requested by the author.

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